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# CHRONIC PASSIVE CONGESTION OF THE LIVER

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BOSTON

In the text-books on pathology a lesion of the liver is described in which the liver cells around the hepatic veins are atrophied and wanting, and the blood spaces are distended and filled with blood. This condition is generally supposed to result from continued pressure on the liver cells due to passive congestion. This continued pressure causes the cells to atrophy and disappear.

Mallory<sup>1</sup> describes a hemorrhagic type of necrosis. In this type an exudate into the spaces occupied by the necrotic liver cells is composed chiefly of red-blood corpuscles. These dilated spaces filled with red-blood corpuscles give the appearance of dilated sinusoids (especially when the necrotic liver cells have more or less disappeared). As a matter of fact, the sinusoids in these cases are practically empty and collapsed.

As a result of recent histologic study of a series of cases Mallory<sup>2</sup> reports that the type of congested liver mentioned in the text-books is not the result of chronic passive congestion only, but that the passive congestion is complicated by a hemorrhagic necrosis around the hepatic veins. In these cases the necrotic liver cells are in various stages of disintegration and disappearance, so that they are readily overlooked. The dilated liver cell spaces filled with blood are commonly mistaken for dilated sinusoids.

The object of this work has been to study the clinical history of a series of cases, in order to see if the clinical picture would support the view that an uncomplicated chronic passive congestion would not show any disappearance of liver cells.

A series of cases was examined which had been treated at the Boston City Hospital and eventually came to autopsy. It soon became apparent that in the majority of cardiac cases of long standing that suffered from broken compensation the liver presented the picture of loss of liver cells around the hepatic veins. The following case is a typical one of this class, of which over a dozen cases were studied.

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\* Published with approval of the Committee on Fellowships as part of the work done under a Bullard Fellowship, Harvard University, 1908-1909.

1. Mallory, F. B. Necrosis of the liver. Jour. Med. Research, 1901, vi, 264.

2. Mallory, F. B. As yet unpublished.

## CHRONIC PASSIVE CONGESTION OF LIVER

In this and subsequent clinical histories only those features are recorded which pertain to the cardiac condition. In the autopsy reports only those parts are recorded which relate to the question of chronic passive congestion. Then the complete anatomic diagnosis is given.

**CASE 1** (Boston City Hospital Autopsy Record, 1905, 122) —*Patient*—A man, 71 years old, entered hospital June 17, 1905. Past history brief, but negative as regards heart. For two years he had had precordial pain off and on, shortness of breath on going up hill, gradually increasing dyspnea and orthopnea.

*Physical Examination*—This showed dyspnea, orthopnea, cyanosis, puffiness of face. Heart slightly enlarged, sounds distant and weak. Rales throughout both lungs, more marked at the bases behind. Liver extended from fourth rib to costal margin, edge not felt. Abdominal wall edematous. Slight dulness in flanks. Considerable edema of legs and thighs. Cyanosis of extremities.

From entrance until July 29, 1905, the patient ran a typical course of gradually increasing cardiac failure and died on that date.

*Autopsy Report*—This showed edema of legs, thighs, scrotum, slight ascites, hydrothorax and hydropericardium. Heart weight was 965 gm. Valve measurements<sup>3</sup>: tricuspid, 16 cm., pulmonic, 10 3/4 cm., mitral, 12 cm., aortic, 9 cm. Except for their size and a few yellowish thickenings on the mitral the valves were normal. There were thrombi in the right auricle and ventricle.

*Anatomic Diagnosis*—General arteriosclerosis, chronic myocarditis, hypertrophy and dilatation of the heart, relative insufficiency of the valves, chronic passive congestion of lungs, spleen, liver and gastrointestinal tract, pulmonary emboli and infarctions, anasarca, cholelithiasis, fatty infiltration of liver, chronic adhesive pleuritis, chronic perisplenitis.

*Microscopic Examination*—The liver showed congestion, especially marked around the hepatic vein with disappearance of liver cells, but on high-power examination the red blood corpuscles were found to be to a large extent in the spaces formerly occupied by the liver cells, also some remains of necrotic liver cells and pigmented cells were present. Therefore, in this case we have a combination of chronic passive congestion and hemorrhagic necrosis.

A series of twelve cases were next studied in which the liver showed congestion, but no disappearance of liver cells. Two of these cases are given below. These cases are the best examples from the series, not just average cases.

**CASE 2** (Boston City Hospital Autopsy Records, 1906, No 113) —*Patient*—A woman, aged 49, entered the Boston City Hospital for the first time Dec 23, 1905. She gave an indefinite history of rheumatism seven years previous. Her present illness had a duration of five months. She complained of pain over the precordia, shortness of breath, orthopnea and cough with abundant yellowish expectoration. Her ankles had also been swollen.

*First Physical Examination*—This revealed an irregular pulse, enlarged heart, and cardiac murmurs. The lungs showed a few rales at the bases. The liver was enlarged by percussion. There was a question of a slight ascites, and there was marked edema of the lower legs.

During the patient's stay in the hospital, until Jan 20, 1906, her heart became more regular, the murmurs became more pronounced, and her edema practically cleared up. On March 20, 1906, she was readmitted to the hospital. She

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<sup>3</sup> These measurements refer to the circumference of the valve, measured at the base of the leaflets after the heart has been opened.

had been pretty well until the last few weeks During this time she had been unable to lie down and has been short of breath

*Second Physical Examination*—This showed cyanosis, dyspnea, orthopnea, an irregular and enlarged heart with double murmurs, signs of fluid in both bases, liver enlarged to percussion, but not felt, ascites and marked edema of the legs On April 14, 1906, the patient's symptoms had improved slightly, but had not disappeared She left the hospital, however On May 22, 1906, she again entered the hospital Since her last discharge she had not been well She could not lie down and she raised considerable yellow sputum tinged with blood

*Third Physical Examination*—Physical examination showed dyspnea, orthopnea and cyanosis The heart was enlarged, irregular and weak with double murmurs There was hydrothorax, ascites and marked edema The size of the liver could not be made out by percussion

On April 29, after a few days of apparent improvement, the patient suddenly died At no time during her stays in the hospital was her temperature elevated except for two days at the time of entrance on the last time

*Autopsy Report*—Rather obese woman Slight edema right hand and foot Marked edema left arm and hand, leg and foot Slight ascites Hydrothorax and hydropericardium Heart, 700 cm Measurements of valves. tricuspid, 13 cm, pulmonic 8.5 cm, mitral, 11.5 cm, aortic, 8.5 cm Myocardium pale Slight thickening of the endocardium over the mitral leaflets No retraction Lungs infarction of the left lower lobe Liver, 2400 gm Vessels engorged

*Anatomic Diagnosis*—Acute pericarditis, acute and chronic pleuritis, hypertrophy and dilatation of the heart, chronic myocarditis, chronic endocarditis, chronic passive congestion of the liver, spleen and kidney, embolus of pulmonary artery, atelectasis of lower lobe left lung and lower part of upper lobe of left lung, ovarian cyst, mucous polyp of the cervix of the uterus, chronic ependymitis, arteriosclerosis, edema of brain, cysts of choroid plexus

*Microscopic Examination*—The liver showed a distention and engorgement of all the sinusoids and blood-vessels with red blood cells There was no apparent diminution in number of the liver cells, or necrosis of liver cells

CASE 3 (Boston City Hospital Autopsy Records, 1907, No 2) —*Patient*—A man, aged 48, entered hospital Oct 19, 1906 Past history brief and negative in regard to the heart Present illness has duration of one month Onset, which was gradual, consisted of shortness of breath Then patient noticed he had to pass urine four to five times at night, also that his feet began to swell and gradually his scrotum

*First Examination*—This showed heart enlarged to the right, action regular, sounds faint, and a faint systolic murmur at apex and an increased pulmonic second sound, liver apparently not enlarged, slight ascites and marked edema of legs, thighs and scrotum The patient's urine showed a good deal of albumin, some blood cells, but no fat

The patient stayed in the hospital until October 31, when, his edema having disappeared, he went home He was considered a case of nephritis of a diffuse type After leaving hospital the patient said he worked until the latter part of December On December 27, 1906, the patient again entered the hospital on account of shortness of breath and swollen legs, which had been coming on for three weeks

*Second Physical Examination*—This showed the following points Cyanosis, heart area which could not be made out Heart sounds weak and no murmurs Edema and pleural fluid at the bases of both lungs, ascites and marked edema of legs, thighs and scrotum The liver dulness was not made out The edema steadily increased until the patient died, Dec 31, 1906 The clinical diagnosis was still

## CHRONIC PASSIVE CONGESTION OF LIVER

a form of nephritis. There was no elevation of the temperature at either of the stays in the hospital.

*Autopsy Report*—Finger-tips blue, marked edema of body, less of face, ascites, hydrothorax, hydropericardium. Heart, 710 gm. Valves normal. Measurements. tricuspid, 13 cm., pulmonic, 8 cm., mitral, 9.5 cm., aortic, 7 cm. Color of myocardium brownish-red with yellow and light gray areas, coronaries slightly thickened.

*Anatomic Diagnosis*—Hypertrophy of heart, general anasarca, cough and edema of lungs, chronic passive congestion of the spleen, liver and kidney, chronic pleurisy, arteriosclerosis, aberrant pancreas, edema and congestion of the brain, cyst of choroid plexus, arteriosclerosis of the basal vessels.

*Microscopic Examination*—The liver showed congestion of the sinusoids and blood vessels with red blood corpuscles, but no diminution of the liver cells or necrosis of them. Kidney showed congestion, some sclerosis of the arteries and thickening of some of the walls of the glomerular capillaries.

From the autopsy findings it seems evident that this was not a case of chronic diffuse nephritis, but that the main cause of the edema lay in the weakened, hypertrophied and somewhat dilated heart.

There is no doubt that in these two cases we are dealing with long-standing cardiac insufficiency. Both of these patients had congestion of the liver. Neither of these cases presented a picture of destruction of the liver cells from long-continued pressure. From these two series it is evident that cases of chronic passive congestion of long standing exist without any disappearance of the liver cells. Furthermore, it is evident that in cases where the liver cells have disappeared this disappearance is due to necrosis and not to continued pressure.

To emphasize the point that necrosis and not long-continued congestion is the primary factor in livers in which the cells have disappeared, the following case is given, which represents a small class of cases studied.

**CASE 4** (Boston City Hospital Autopsy Record, 1907, No. 37) —*Patient*—A man, aged 65, entered hospital Jan 26, 1907. His past history is brief and negative as regards the heart. His present illness is of eleven days' duration, and started with a sudden attack of dyspnea and with a cough accompanied by a thick white sputum. He has had three chills in three weeks, some pain over the precordia. He has noticed no swelling of the legs.

*Physical Examination*—This showed marked prostration and dyspnea. Pulses regular and Corrigan in type. Heart slightly enlarged with a regular action and diastolic murmur, denoting a leak at the aortic valve. The lungs showed a diffuse bronchitis, but no edema at bases. The liver extended from the sixth rib to the costal margin. Its edge was not felt. There was no edema. After five days in the hospital without appreciable change a sudden acute general edema of the lungs developed and the patient died.

*Autopsy Report*—No edema, 400 cc. slightly peritoneal fluid. Heart, 760 gm. Cavities very large. Aortic valve, many small white calcified masses. Other valves normal in appearance. Measurements of valves: tricuspid, 14 cm., pulmonic, 9 cm., mitral, 11.3 cm., aortic, 8.5 cm. Liver weight, 1700 gm., dark brown in color with increased consistency, markings very distinct. Weight of kidneys, 350 gm. Each kidney has a few cysts. The glomeruli visible. Capsule strips easily.

*Anatomic Diagnosis*—Hypertrophy and dilatation of heart, chronic nephritis, bronchopneumonia, chronic pleuritis, edema and congestion of lungs, slight chronic endocarditis, arteriosclerosis, double inguinal hernia, chronic localized peritonitis, subpial edema, cyst of choroid, arteriosclerosis of basal vessels

*Microscopic Examination*—The liver is not especially congested throughout. There is quite an extensive necrosis of the liver cells around the central veins. Near the central veins around these necrotic cells the red blood cells are filling the sinusoids and also the spaces occupied by the necrotic and shrunken liver cells, and also spaces from which the liver cells seem to have disappeared. Kidney. Some of the glomeruli are sclerotic with a slight amount of lymphocytic infiltration and slight increase of connective tissue. Much of the tubular epithelium is granular with an occasional cast.

Here we have a case of an enlarged heart apparently due to arteriosclerosis or to chronic nephritis of long standing. The heart, however, has never shown broken compensation, and that it has been able to do its work well is shown by the fact that there was never any edema and that microscopically the liver was not especially congested. Still, in this case there is the appearance around the central veins of congestion and disappearance of liver cells. In other places, however, where there is no congestion, the liver cells around the hepatic vein are necrotic, and these necrotic cells are in such numbers that it is impossible to record their death as due to anything short of a toxin. In other words, this is a typical case of central necrosis due to toxins, but it is complicated by being of the hemorrhagic type in many places, and therefore closely resembles the picture considered characteristic of chronic passive congestion. Although no especial study has been made of the point, it has been noted that this form of hemorrhagic necrosis has been met with only in cases in which there is some disturbance of the circulation.

From these cases the following conclusions seem justifiable. Uncomplicated chronic passive congestion of the liver, even in cases of long standing, does not necessarily lead to atrophy and disappearance of liver cells. It is, therefore, possible to imagine their disappearance in other cases as due to something else than long-continued congestion. Hemorrhagic necrosis of the liver is a very frequent complication of chronic passive congestion of the liver. This form of liver necrosis probably occurs only in cases with some degree of cardiac insufficiency.

# CHRONIC ALEUCEMIC ENLARGEMENT OF THE LYMPHATIC GLANDS

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Our only excuse for adding to the already overburdened literature of the pathology of the lymphatic glands is the belief that there is still need for long and careful observation on cases of any disease of this system, but more especially of the group originally designated by the term "pseudoleucemia". Our knowledge of this group has reached the point where one case, studied carefully by the clinician in conjunction with the pathologist, is of more value than a large series of cases drawn from the average medical, surgical and pathological records, which are not complete in all the necessary details.<sup>1</sup>

## HISTORY OF CASE

*Patient*—An unmarried white woman, J G, aged 29, was admitted to the Montreal General Hospital, Oct 20, 1907, complaining of weakness, loss of weight, enlargement of the glands, morning chills and pain in the left side of the abdomen. The patient was born in Ireland, but had lived in Canada ten years where she was engaged in housework. Though she had never been robust, there was nothing in either the personal or the family history which suggested tuberculosis. She had acute articular rheumatism at 9 years of age, which, owing to the pain and swelling in both ankles, incapacitated her for six weeks. The use of alcohol or other drug was denied, and there was no history of lues. On Oct 17, 1905, she had had a full-term child with instrumental delivery and without special hemorrhage. In November, 1906, the patient had an attack of "muscular rheumatism" which lasted for six months and which confined her to bed for some weeks on account of aching pains in the muscles of the right arm and shoulder and the right leg, the pain was worse at night and on movement. The muscles were very tender but there was no swelling or redness.

*Present Illness*—This began in April, 1907, when the patient was again forced to go to bed on account of weakness, chilly sensations and night sweats. Vomiting preceded by slight epigastric pain occurred each morning after breakfast. Constipation was persistent. There was no hematemesis. Chills followed by sweating became frequent, occurring day or night and varying in duration from a

\* From the Clinical and Pathological Laboratories of the Montreal General Hospital

<sup>1</sup> We wish to thank Dr F G Finley, who kindly afforded us the opportunity of studying the case.

few minutes to two hours In July, 1907, the patient first noticed enlargement of the glands in the right side of the neck and subsequently in the right axilla and the left side of the neck The glands were very tender, at times painful, but never broke down There was no cough or expectoration, but cardiac palpitation occurred on exertion Dysmenorrhea was present from July, 1907 The appetite steadily failed and the patient grew gradually weaker She had lost 35 pounds in weight in twelve months She had become very nervous and irritable and had been unable to work since the onset of her illness

*Physical Examination* (October 20, 1907) —The patient was found to be well developed but poorly nourished. The face and mucous membranes were pale and the skin moist The bones and joints were normal The thorax was well formed except for slight flattening in the right infraclavicular region The lungs were resonant throughout, and the breath sounds were vesicular The circulatory system was negative The tongue was pale but clean The abdomen was flat and soft The liver was not enlarged The firm edge of the spleen was just felt at the costal border The urine was straw-colored, acid, sp gr 1017, and contained neither albumin nor sugar, microscopically it showed epithelial débris and a few pus cells The temperature ranged between 99.2 and 101.4 F and the pulse between 88 and 108

*Glandular System* All the superficial glands were enlarged, firm, discrete, freely movable, not adherent to the skin, and slightly tender The posterior and anterior cervical glands on both sides were markedly enlarged, varying from the size of a small bean to that of a hazelnut The right posterior auricular glands were about the size of a pea, while the supraclavicular glands on both sides were about the size of a bean In the right axilla the glands were the size of marbles and formed a regular chain along the border of the pectoral muscles, in the left axilla only one or two glands were to be felt The right inguinal glands were moderately enlarged The left epitrochlear gland was also palpable The mediastinal glands were enlarged, as shown by dulness over the manubrium and upper portion of the sternum, extending laterally 6.5 cm to the right and 3.5 cm to the left of the midsternal line, and downward from the episternal notch to merge with the cardiac dulness below The retroperitoneal glands were not palpable

*Course of Disease* —On October 21 the blood examination revealed a moderate secondary anemia with slight leucocytosis, and a tentative diagnosis of Hodgkin's disease was made

On October 23 two glands were removed from the neck for microscopic examination On three other occasions during the course of the succeeding ten months glands were removed for histological study The sections showed the histopathological picture described by Dr Dorothy Reed

Repeated blood examinations were made which will be discussed subsequently, suffice it to say that there was always a slight secondary anemia which increased as the disease advanced There was also a slight but definite leucocytosis The Widal test and blood cultures proved negative The eye-grounds were normal After a short period of apyrexia during the second week after admission, there developed an irregular, intermittent fever ranging between 98 in the morning and 102 F in the afternoon Fairly profuse sweats occurred daily Chilly sensations were occasionally complained of, but there were no actual rigors

By January, 1908, the glands on the right side of the neck had increased to about the size of a hen's egg The dulness over the manubrium and the splenic enlargement persisted The color was strikingly pale and out of all proportion to the hemoglobin defect This, with the general glandular enlargement, presented an unusual picture On March 2 the Calmette reaction was negative On March 4 the spleen was noted to be larger, reaching three fingers' breadth below the costal border, the edge was very firm and the surface felt irregular

## ALEUCEMIC ENLARGEMENT OF LYMPH GLANDS

On May 7 the patient was noted to be gradually failing, the color had become more and more waxy, suggesting the white type of pernicious anemia. The gums and mucous membranes appeared almost bloodless and the tongue the color of pork. The tonsils were slightly enlarged. There was brownish desquamation over the trunk (arsenical) but no special pigmentation of the axilla or mouth. A general pruritus was very troublesome. All the superficial glands had diminished until the cervical glands were about the size of cherries, the axillary about the size of marbles and the epitrochlear of split peas, the inguinal varied from the size of a pea to that of a silbert. The dulness over the manubrium was not so extensive. There were no retroperitoneal glands palpable. The abdomen was strikingly full as compared with the patient's emaciation, owing to the presence of ascites. The liver was not enlarged but the spleen reached to the level of the

TABLE OF BLOOD EXAMINATIONS

Date	R B C per c mm	Per ct Hb (Sphl)	Index	W B C per c mm	Per cent P neut	Per cent L ymph	Per cent Sm monocytes	Large lymph	Large and transit monocytes	Per cent Lympho- cytes	Mast- cells	Per cent Ery- throblasts	Remarks
10/21/07	3,820,000	52	0.7	12,720	71.0	7.8	6.0	13.6	0.1	0.8	0.4		No polikilocytosis, no erythroblasts
11/20/07	4,160,000	50	0.6	19,760	88.2	2.8	2.6	6.0	0.2	0.0	0.2		No polikilocytosis, no erythroblasts
12/30/07	3,815,000	50	0.65	20,760	89.0	1.4	0.6	5.4	0.4	0.2	0.0		No polikilocytosis, no erythroblasts
1/30/08	3,590,000	55	0.7	19,800	87.4	6.1	3.0	2.6	0.6	0.0	0.0		No polikilocytosis, no erythroblasts
3/4/08	3,320,000	54	0.9	21,600	88.4	8.2	1.8	1.4	0.0	0.0	0.0		0.2 per cent Tirk's giant cells, no erythroblasts Smears lost
5/10/08	2,300,000	41	0.9	14,400									
5/20/08				10,280	71.0	24.4	2.0	1.2	0.0	0.0	1.4		Two normoblasts in count of 500 cells
6/20/08	1,260,000	20	0.8	16,840	79.2	17.6	1.8	0.6	0.4	0.0	0.4		Macrocytes and microcytes, polikilocytosis and polychromatophilia 18 normoblasts and 1 intermediate cell in 500 cell count
6/29/08	1,084,000	20	0.9					.					
7/31/08	1,801,000	32	0.8	8,800	67.2	29.0	1.6	1.6	0.2	0.0	0.4		Macrocytes and microcytes polikilocytosis and polychromatophilia, 8 normoblasts and 1 intermediate cell

umbilicus in the midclavicular line, the edge was thin, sharp and notched and two irregularities were felt on the surface. There was slight tenderness on percussion over the tibiae and femora.

On August 2 the patient's condition was noted to be grave. There was profuse diarrhea. Emaciation was extreme and the pallor striking. The temperature had become subnormal. There had been a further diminution in the size of the glands, none were larger than an almond and there was no longer dulness over the manubrium. The spleen could no longer be felt. The patient gradually sank and died on the morning of August 5.

*Treatment*—After admission various tonic and supporting methods of treatment were tried [including, owing to the possibility of syphilis being the etiological factor, a prolonged course of potassium iodid in doses up to 30 grains three times a day], all without effect on the course of the disease, subsequently iron and arsenic were given without apparent benefit.

*The Blood*—Blood examinations were made at intervals of one month. The hemoglobin percentage, which was estimated by Sahli's instrument, was considerably below normal, and always lower than the percentage of red cells. The latter showed a slight but definite diminution until shortly before death, when a marked anemia existed. The color index at first was very low, but as the anemia progressed it rose until it reached 0.9, the anemia was therefore of a progressive secondary type. The usual stigmata of a severe anemia were absent for the first four months, after which a few normoblasts appeared. During the last two months of life macrocytes, microcytes, polikilocytes, polychromatophils and a considerable number of normoblasts were observed, with an occasional intermediate type of erythroblast, but megaloblasts were never noted. There was, therefore, a considerable derangement of the erythropoietic mechanism.

A slight leucocytosis was present. This at first was due to an increase of the non-granular mononuclear cells, but later to an increase in the polymorphonuclear neutrophils.<sup>2</sup> Three types of the non-granular mononucleairs were present, namely:

1. Small lymphocytes, i.e., the typical small non-granular cell about the size of a red blood cell with deeply staining basophilic nucleus and narrow rim of deeply staining protoplasm, these cells were for months markedly diminished in number, and it was only towards the end of the disease that they reached normal limits.

2 Large lymphocytes of Ehrlich, i.e., cells in every way resembling the former except in their size, which varied from a little less to a little greater than the polymorphonuclear cell, they were always present and at first formed 6.0 per cent of the total white count. These cells are considered by Ehrlich to be present in small numbers normally and are to be differentiated from the myeloblasts (Naegeli) or unripe cell (Grawitz) present only in pathological blood. They were, however, in this case, at least in the beginning, above the normal limits.

3 Large mononuclear and transitional cells, the former were voluminous cells with a diameter two or three times that of a red cell with a round, feebly staining nucleus and a relatively large amount of non-granular, weakly basophilic protoplasm. The transitional cells were similar except for a kidney-shaped or indented nucleus and the presence of a few neutrophilic granules. These two types, which were grouped together, were at the first examination markedly increased in number, but gradually diminished during the subsequent four months until they reached the normal limits.

Myelocytes of the neutrophilic variety were on several occasions found in small numbers and presented the usual characteristics. No eosinophilic myelocytes were found. The polymorphonuclear neutrophils, which on first count were relatively diminished, later became relatively and absolutely increased, and finally, before death, relatively and absolutely diminished. The polymorphonuclear eosinophils, in spite of their enormous increase in the glands, were not increased in number in the blood. Mast-cells or the polymorphonuclear basophils were normal or absent. On one occasion a single "Turk giant cell" was found, i.e., a very large mononuclear cell with a round eccentric nucleus and a deeply staining reticular protoplasm.

Hence there was present in the course of the disease a moderate leucocytosis due at first to a lymphocytosis of the large celled variety as was first noted in this condition by Ehrlich and Pinkus. Subsequently a slight polymorphonuclear leucocytosis was present, as is usual in this group of cases. Before death this

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2 The stain usually employed was Wright's modification of the Romanowski, but on several occasions Ehrlich's triacid stain was used in confirmation.

latter leucocytosis was replaced by a normal leucocyte count with a moderate small celled lymphocytosis

*Autopsy*.—This was performed on Aug 5, 1908, eight hours after death and thirteen months after the onset of the glandular enlargement

The body was that of a fairly well developed but markedly emaciated white woman. The mucous membranes were very pale and there was slight edema about the ankles and the right hand. No rigor mortis was present. The lymph glands were distinctly palpable in the neck, axilla and groins.

The brain, cord and meninges appeared normal. The bone marrow removed from the middle of the femur was of the red variety, quite firm, and heavily flecked with fatty tissue.

The pleurae were normal. The lungs were voluminous and crepitant, with slight emphysema at both apices, nowhere was there congestion or edema. The mediastinal and bronchial lymph glands were greatly enlarged, averaging 2 by 1 cm in diameter. On section they were of a uniformly reddish pink color except where they were deeply stained by carbon pigment. Nowhere was there gross evidence of tuberculosis.

The pericardium was normal and the heart, though small and flabby, showed no gross lesion.

The peritoneal cavity contained 25 liters of slightly turbid fluid. The parietal and visceral peritoneum was smooth and glistening, and free from adhesions. The mesenteric lymph nodes were slightly increased in size, while the retroperitoneal nodes were markedly enlarged and quite firm. The largest glands were found about the lesser curvature of the stomach. No hemolymph glands were discernible.

The gastro intestinal tract was normal except for the lymphoid structures which were swollen and pigmented.

The liver weighed 1020 grams, it was pale and flabby. On section the organ presented the normal gross appearances. The ducts and gall-bladder were normal.

The spleen weighed 335 grams, it was very firm and irregularly nodular. The nodules ranged from the size of a pea to that of a small marble. On section some of the nodules appeared firm and dark red in color, while others were pure white and sharply defined. The Malpighian bodies were obscured. No splenic pulp came away on scraping.

The kidneys weighed 300 grams, their capsules stripped readily. On section the normal markings were poorly defined. The Malpighian tufts were not visible.

The pancreas, adrenals and genito urinary organs were normal.

*Anatomical Diagnosis*.—Hodgkin's disease, general glandular enlargement, acute and chronic splenitis, anasarca, fatty degeneration of the heart, chronic interstitial nephritis, lymphoid metaplasia of femoral marrow.

#### HISTOLOGY

For histological study the tissues were fixed in Zenker's fluid, alcohol, and formalin, and embedded in paraffin. Eosin methylene blue, hematoxylin and eosin, and Mallory's connective tissue stains were employed in the routine staining of the sections.

In the following histological descriptions the organs will be considered separately.

*Lungs*.—Normal except for a slight peribronchial pigmentation.

*Heart*.—There is an absence of the epicardial layer of fat. The muscle fibers show in areas a preference for the eosin stain. The striations are poorly defined and often lost, while the fibers are swollen, granular, and contain fat vacuoles as shown by the Scharlach-R stain in formalin-fixed sections. This fatty

degeneration is rather diffuse. There is also an occasional patch of fibrosis replacing wholly, or in part, the muscle fibers.

*Kidneys*—The cortex shows a few isolated areas of dense, fibrous connective tissue in which the renal tubules are almost completely absent. Here and there in the medulla the epithelium of the convoluted tubules is swollen and finely granular.

*Uterus and Ovaries*—There is a moderate degree of intimal and medial thickening of the vessels.

*Pancreas*—This shows an increase of the interlobular connective tissue. The smaller vessels are injected and there is a moderate grade of perivascular lymphocytic infiltration.

*Liver*—The vessels are moderately injected. The caudal cells are almost uniformly cloudy and many of them contain pigment. An occasional vessel shows a perivascular infiltration of mononuclear leucocytes and a few eosinophils, no large mononuclear or multinuclear cells are present.

*Small Intestine*—The mucosa is covered with an extensive membrane which in places shows beginning organization. The submucosa is uniformly thickened by edematous connective tissue. The mucosa is completely lost in places and presents the picture of a healed ulcer. Some of the lymphatics are dilated and filled with cells, chiefly of the mononuclear variety. In the interstices of the submucosa, especially where the edema is most marked, are numerous polymorphonuclear neutrophils. Both muscular coats and the serosa are normal. The lymph follicles are negative.

*Spleen*—There is slight congestion. The Malpighian bodies are few and poorly defined, some are riddled with intercommunicating bands of newly-formed connective tissue. Infiltrating these connective tissue bands, and, generally speaking, confined to these areas, are fairly numerous eosinophils averaging about 17 cells to a microscopic field (ocular 4, objective 1/12). Other Malpighian bodies show areas of large cells which stain more lightly than the lymphoid cells and contain a considerable amount of altered blood pigment. No giant cells are seen in the sections. The fibrous tissue is usually increased about the periphery of the gland, gradually replacing the Malpighian bodies until there are but a few cells immediately surrounding the central vessels. Other Malpighian bodies are completely obliterated by the fibrous tissue encapsulation, though the central vessels remain apparently unaffected.

The pulp is riddled with fibrous tissue. The blood-spaces, in the main, are narrowed into mere slits or are completely obliterated by cicatricial tissue. There is apparent a compensatory enlargement of the surviving blood-channels. The plasma cells are greatly diminished in number. Neither mast-cells nor myelocytes are found. Only after a long search is a collection of normoblasts found in conjunction with a few eosinophils and plasma cells, elsewhere normoblasts are found singly or in pairs. Some sections show old, anemic infarcts, surrounded by a broad zone of hemorrhage.

*Bone Marrow*—The bone marrow from the femur presents the red marrow or lymphoid type, the fatty portion is for the most part replaced by cellular tissue. The vessels are distended with blood. There are the usual foci of erythroblasts, entirely of the normoblastic type. Neutrophilic myelocytes are present in the normal proportion. The eosinophilic type of myelocyte is perhaps unusually preponderant. The large lymphocytes or premyelocytes are also quite numerous. There are many polymorphonuclear neutrophils and eosinophils. One or two giant marrow cells are found but no mast-cells. Two or three foci of lymphocytes are seen in which there are a few uninuclear and binuclear giant cells, without evidence of nuclear division.

*Lymphatic Glands*—Six glands were removed from either the axilla or neck on four different occasions during the course of the disease—four, five, nine and ten months after the glandular enlargement was first noticed by the patient. The progress of the disease process, as shown by the histological picture, did not always correspond with the time of the removal of the gland, as some of the glands first examined were in a more advanced stage than were those subsequently removed. At the autopsy glands were procured from the cervical, axillary, mediastinal, peribronchial and retroperitoneal regions. Sections from thirteen of the glands removed at the post-mortem, together with the six removed during the course of the disease supplied the material for study.

The glands were irregularly oval in shape and were easily dissected away from one another and from the surrounding tissues. In consistency they were firm and elastic, and varied in size from 4 cm to 0.5 cm in diameter. No very large glands were found, though on the whole those removed during life were larger than those found at autopsy. At no time was there evidence of softening or fluctuation. On section they were of a uniformly gray or reddish pink color, semitranslucent and often distinctly lobulated, the cut surface was granular but did not exude blood or other cellular material. There were no gross evidences of tuberculosis, such as caseation or calcification.

There are two very striking points in the microscopical picture, viz (1) The invasion and subsequent obliteration of the normal gland structure by connective tissue and (2) the presence of abnormal cells.

The condition of the gland capsule varies greatly, in some sections it is very distinct and uniformly thickened to many times the normal, in others there is no definite capsule but a dense, irregular mass of fibrous tissue which is apparently the result of both a periglandular and an intraglandular increase. As a rule, the capsule remains well defined in the early period of the disease, in the later stages, however, it invades the gland tissue. In most glands the trabeculae are more numerous, larger and thicker than normal, in the last stages of the process they present evidence of advanced, hyaline degeneration.

The normal structure of the gland is either markedly altered or entirely lost, depending on the stage of the disease. The outer lymph channel is partially or completely obliterated by fibrous connective tissue. The internal lymph channels are either blocked by abnormal cells or narrowed by the new growth of connective tissue. Late in the course of the disease surviving lymph channels are often found enormously dilated and the germinal centers are with difficulty recognized, though possibly the latter are the last to be invaded by the fibrous tissue, they are often so altered as to be readily overlooked. In none of the glands is there either evidence of active proliferation in the germinal centers or increase in the lymphadenomatous tissue proper, as noted in the glands during the earliest stages of the disease by Reed and Longcope. No doubt this early stage had been succeeded by another which, though the earliest stage observed in our case, was not the first development of the disease process. The enlargement of the glands is primarily due to the presence of abnormal cells. Furthermore, in no stage of the disease is there any evidence of the gland parenchyma infiltrating beyond the capsule as is the rule in lymphosarcoma. The new tissue consists of (1) proliferated endothelial cells, (2) mononuclear and multinuclear giant cells, (3) eosinophils, and (4) fibrous connective tissue. These will be discussed in detail.

1 Large Endothelial Cells (the epithelioid cells of Reed). These are large cells several times the diameter of the lymphocytes, and more suggestive of the pale staining cells with vesicular nuclei which occur in the center of the germinal nodules of lymph-glands and the Malpighian bodies of the spleen in certain acute infectious diseases. They have an ovoid or vesicular nucleus with a distinct nucleolus and an abundant non-granular, lightly staining protoplasm, they lie in the main in the lymph channels and often form a mosaic. As a rule they are

more numerous in the fields where there is little or no increase in the connective tissue. It would seem that these cells take their origin from the endothelium of the lymph channels and spaces. In one section many of the lymphatics are occluded by the endothelial cells, while in another section a typical mononuclear cell is found still attached to the wall of the vessel (Fig 2), and in yet another field a large mononuclear cell is fixed in the act of passing through the wall of the vessel.

**2 Mononuclear and Multinuclear Giant Cells** All stages in development from the large mononuclear cells to still larger mononuclear and multinuclear giant cells can be traced. The cell protoplasm is irregular in outline, non-granular and pale staining. The multinuclear cells contain several nuclei varying from three to eight in number. These nuclei are heaped together centrally or peripherally but never with the discrete and regular peripheral arrangement so characteristic of the giant cell in tuberculosis. The nuclei stain deeply, are rich in chromatin, and contain one or several well-defined, deeply staining nucleoli. Many of these giant cells show karyokinetic figures. It is evident that these cells become multinucleated by a process of amitosis. In one section they occur free in the lumen of the blood-vessels. In the glands of the more advanced stages many of the giant cells have apparently reached their maximum development and show evidence of protoplasmic degeneration and fragmentation of the nuclei. Their occurrence not only in the lymph channels but everywhere throughout the gland parenchyma, their nuclear structure and their staining reactions, suggest an endothelial origin. No "islands of syncytium" as described by Weishaupt and Longcope are found.

**3 Eosinophils** In nearly all the glands in the early stages of the disease the eosinophils are very numerous. In some parts of a section, under low magnification, they give the impression of an entirely red field. They are almost always to be found in relation with the new fibrous connective tissue and form a "rear-guard," as it were, to the latter. They become less numerous as fibrosis becomes more complete. Occasionally they are present in groups independently of any special fibrous tissue growth. They are all polymorphonuclear cells of the type found in the circulating blood, none are seen resembling in size or morphology the myelocytic eosinophil (Fig 4).

**4 Fibrous Connective Tissue** Even in the earliest stage studied by us there is an increase in the fibrous connective tissue. This seems to have its origin in the gland capsule and its trabeculae. In some glands the primary increase in the connective tissue is about the outer lymph sinus from which the subsequent invasion of the gland parenchyma has its origin. It gradually invades the parenchyma, pushing it aside and replacing it until only islands of lymphadenomatous tissue remain. Finally these islands become barely discernible. All stages in the development of connective tissue, from the youngest fibroblasts to dense connective tissue, are well shown by Mallory's connective tissue stain. This differential stain also furnishes proof that the fibrosis begins at the periphery and gradually works inward, and that the germinal centers are the last to be sclerosed. The connective tissue is in places quite cellular but almost always free from a lymphoid and plasma cell infiltration. Sometimes there are seen newly formed vessels within the young connective tissue.

**Plasma Cells** These are only occasionally present in an appreciable number, and as a rule are absent. Only in one gland from the early stage of the disease are they markedly increased. Many of them contain mitotic figures.

**Polymorphonuclear Leucocytes** These are in the majority of glands singularly scarce, though in one gland removed early in the disease they exist in considerable numbers and occur in definite foci.

**Phagocytic Cells** In some connective tissue areas of certain glands there are moderate numbers of endothelial cells which are phagocytic for blood pigment

**Blood-vessels** In the early stages of the disease the larger vessels of the glands show edema of the walls. In the later stages many of the arteries and an occasional vein are greatly distorted and contain focal lesions in the intima and media, one large vessel shows calcareous deposits in the media and to a less extent in the intima. The intimal lesion is invariably of a focal, proliferative character. There is partial and sometimes complete obliteration of many of the larger vessels in the more advanced stages of the disease. In one or two glands there is evidence of recent hemorrhages into the gland substance. Occasionally there occurs a perivascular infiltration of lymphoid and plasma cells in which are numerous cells containing blood pigment.

Nowhere are there concentric foci of epithelioid cells giant cells of the Langhans type, necrosis or other evidence of tuberculosis. In one section there is found embedded in the connective tissue of the periphery of the gland a large multinuclear giant cell which more closely resembles a "foreign body giant cell" than the usual typical multinuclear cell above described, it is surrounded by a circumscribed area of lymphocytes but without epithelioid cells or evidences of necrosis.

To generalize, then, the disease process as seen by us can be divided into four stages, some of which are illustrated at times in the same gland, but more often in different glands. The earlier stages are best seen in the glands removed during life, but occasionally a gland is found at autopsy which shows the early stage of the process. The earliest stage described by Reed and Longcope, namely, the hyperplasia of the lymphadenomatous tissue, is not seen in our case.

**First Stage**—Here the striking feature is the great number of large mononuclear cells and their development into the larger mononuclear giant cells which often form collections in the gland parenchyma, presenting a picture not unlike the Graafian follicles in the cortex of the fetal ovary. In addition, one sees great numbers of eosinophilic cells and some fibrous connective tissue invasion, though the normal structure of the gland is at this stage well preserved. In this period plasma cells are also numerous and are still actively increasing, as evidenced by mitotic figures. The increase in the size of the glands was undoubtedly due to these cells and not to the essential lymphadenoid tissue (See Figs 1 and 2).

**Second Stage**—This is characterized by fewer mononuclear cells and greater numbers of their derivative multinuclear giant cells which are especially evident in the germinal centers. Their nuclei present every evidence of active division. Eosinophils are also very numerous. New fibrous tissue is now beginning to invade the parenchyma. The disease process would appear to reach the height of development in this stage (Fig 3). From now on the glands gradually diminish in size *pari passu* with the contraction of the fibrous tissue.

**Third Stage**—In this stage one sees fewer multinuclear cells, except, however, in the germinal centers. As a rule these cells have reached full development as shown by the total absence of nuclear figures. There is more fibrosis and consequently less gland structure. The lymphadenoid tissue is the first to yield to the connective tissue invasion, the lymphoid cells have lost their normal staining reaction, the nuclei are fragmented, and the abnormal cells are rapidly disappearing. The eosinophils are distinctly fewer and in some sections difficult to find. The vessels, too, show a more advanced degree of obliterative endarteritis (Fig 5).

**Fourth Stage**—Finally there is almost complete replacement of the gland parenchyma by fibrous connective tissue. The mononuclear and multinuclear giant cells have almost completely disappeared. Some glands show little islets of parenchyma with a more or less normal lymphadenomatous structure and a few

multinuclear or even mononuclear giant cells and eosinophils. These islets, we believe, are the original germinal centers of the gland, which, though the first to show the presence of the characteristic endothelioid and giant cells, are the last structures to undergo fibrosis. The eosinophils are totally absent in the scar tissue proper, but persist in the small areas of gland tissue which have recently undergone fibrosis. The fibrous tissue is, as a rule, denser, more contracted and less cellular than in the previous stage. There is often an enormous dilatation of the surviving lymph channels. The trabeculae sometimes show an advanced stage of hyaline degeneration. Further, in glands where fibrosis is very marked, there are zones of fibrous tissue showing distinct degeneration (Fig. 6).

#### BACTERIOLOGY

Material planted on modified Dorset egg medium and blood-agar slants from the glands during life and at autopsy proved negative. Portions of several glands were emulsified and injected subcutaneously and intraperitoneally into guinea-pigs, but without the development of tuberculous lesions. Lastly, sections from glands both in the early and late stages of the disease were stained for bacteria, notably for tubercle bacilli, but without result.

#### DIAGNOSIS

The various possibilities suggested by the foregoing case were lymphatic leucemia, pseudoleucemia (Cohnheim), lymphosarcoma, Hodgkin's disease, tuberculosis and syphilis.

*Lymphatic Leucemia*—Clinically our case in many ways suggested this condition, the insidious onset, the pallor and secondary anemia and the generalized lymphatic enlargement. Opposed to this diagnosis were the absence of a marked leucocytosis and especially the absence of the typical leucemic blood formula. Furthermore, the histology of the glands removed during life and the complete post-mortem examination presented a picture quite distinct from pure lymphadenoid hyperplasia.

*Pseudoleucemia* (Cohnheim)—Under this term we would include only those cases which resemble typical lymphatic leucemia in every respect except for the absence of a leucocytosis. This term should be confined to those cases which are followed from early in their course to autopsy, for it is now well recognized that lymphatic as well as myelogenous leucemia may have subleucemic or even aleucemic periods when the number of leucocytes is within the limits of normal, though the blood formula may still be a pathological one. Now, as a case of true pseudoleucemia may exhibit a slight leucocytosis with a relative or even absolute lymphocytosis, the close relation, if not the identity, of lymphatic leucemia and pseudoleucemia is very evident indeed in both there is the same lymphadenoid hyperplasia, but in the former there is an absence of marked leucocytosis throughout the disease. There were many points clinically in our case suggesting the diagnosis of pseudoleucemia, which was excluded by the histological examination of the first gland removed.

*Lymphosarcoma*—This was excluded clinically by the absence of regional distribution so much emphasized by Kundrat, and by the discreteness of the glands; anatomically the process affected only the lymphadenoid tissue, not the serous surfaces, periosteum or muscles. The histological picture of the first gland removed suggested to one of us the possibility of a lymphosarcomatous process, however, further study of the glands failed to reveal any invasion of the gland capsule or other evidence of an aggressive character so diagnostic of this condition. The presence of large numbers of eosinophils and the peculiar type of giant cell, together with the fibrosis, were further points against lymphosarcoma.

*Hodgkin's Disease*.—Clinically, and subsequently pathologically, this was the diagnosis made. However one may object to the term "Hodgkin's disease" on account of the variety of different pathological conditions originally included under it, we believe that the picture described by Fischer, Reed, Longcope and MacCallum<sup>3</sup> forms a distinct clinical and histological entity, and that to it belongs our case. The clinical picture of the case reported was not quite usual on account of the diffuseness and uniformity of the glandular enlargement upon the patient's admission to the hospital. Furthermore, not even at the height of the glandular enlargement were there those huge masses in the neck or axilla so frequently seen in the disease. Lastly, the retrogression in the size of the glands and spleen some weeks before death was peculiar. The slight lymphocytosis was quite in accordance with Pinkus' observations, the polymorphonuclear leucocytosis which subsequently developed is the more usual phenomenon, according to Schur. The points in this histological study were (1) a proliferation of large endothelioid cells, (2) the presence of mononuclear and multinuclear giant cells of a peculiar type, (3) the presence of enormous numbers of eosinophils, (4) an early invasion and an ultimate replacement of the gland parenchyma by fibrous connective tissue, (5) the absence of necrosis, caseation, Langhans' giant cells and tubercle bacilli.

We believe, then, that the above-enumerated histological features form a distinctive picture and one which must receive general recognition, call it by whatever name one will. The original objections of Steinberg, Crowder and Schur, who, from the presence of undoubted evidences of tuberculosis in a certain number of their cases, concluded that the whole histological picture was due to the tubercle bacillus, is no longer tenable. For if tuberculosis may be a complication (i.e., secondary infection) or an associated condition in both lymphatic leucemia and pseudoleucemia, why not, too, in Hodgkin's disease? Further, in Fischer's series of twelve cases, inoculation experiments were negative in all. In Reed's<sup>4</sup> series of 8 cases, only one was found with an associated tuberculosis, and that one of a terminal acute miliary type. None of Longcope's<sup>5</sup> 8 cases proved tuberculous. Though Simmons<sup>6</sup> found tubercles in the viscera of 3 of his 9 patients, in 5 of the 6 other cases inoculation experiments proved negative. Hirschfeld's<sup>7</sup> 5 cases were negative histologically and also after injection into guinea-pigs. We agree, therefore, with Longcope, who writes that "when tuberculosis occurs in connection with Hodgkin's disease it can only be regarded as a secondary infection." Sternberg's<sup>8</sup> more recent modification of his original views which assigned the chief rôle to the toxins of the tubercle bacillus, admits

3 MacCallum Johns Hopkins Hosp Bull, 1907, xviii

4 Reed Johns Hopkins Hosp Rep, 1902, x, 133

5 Longcope Bull Ayer Clinical Lab No 1, 1903, p 4

6 Simmons Jour Med Research, 1903, ix, 378

7 Hirschfeld Abstr in Folia haematol, 1909, vii, 151

8 Sternberg Ergebn d Path, 1905, vii, 502

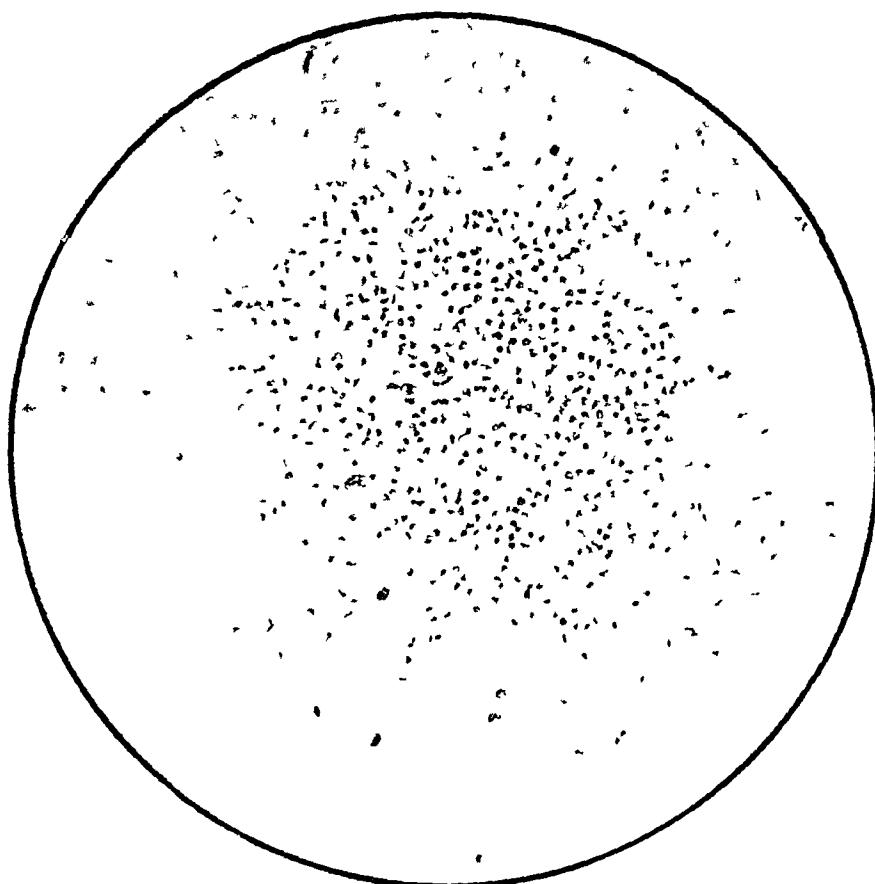


Fig 1.—Stage I Endothelial and mononuclear giant cells

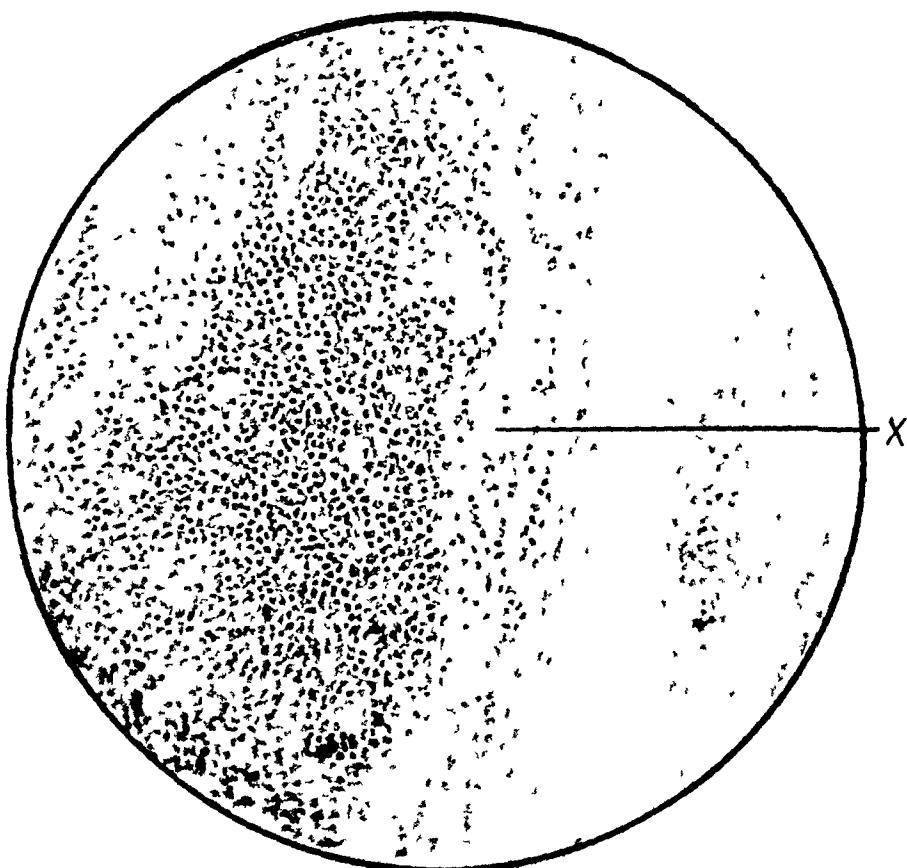


Fig 2.—Stage I Showing origin of giant cell from endothelium of lymphatic

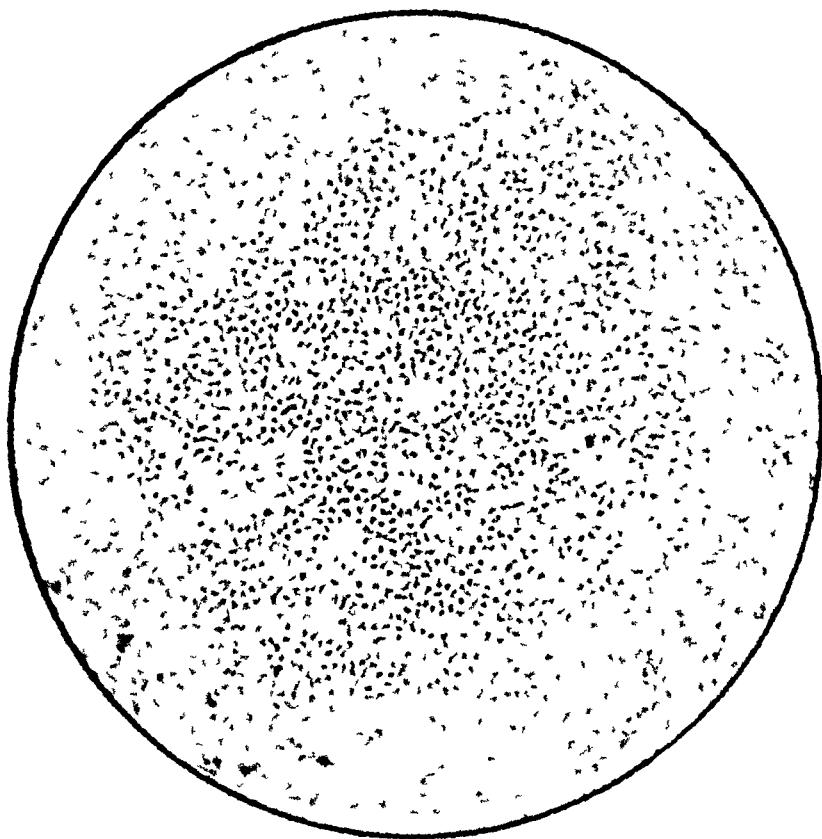


Fig. 3—Stage II Multinuclear giant cells in a germinal nodule

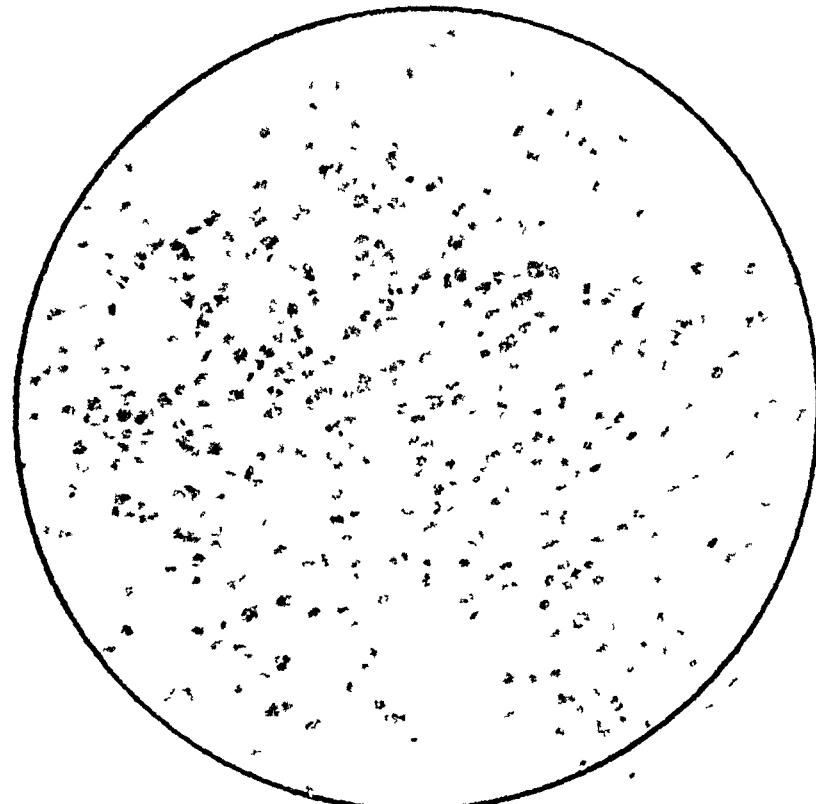


Fig. 4—Stages I and II Eosinophils, recognizable by large coarse granulations

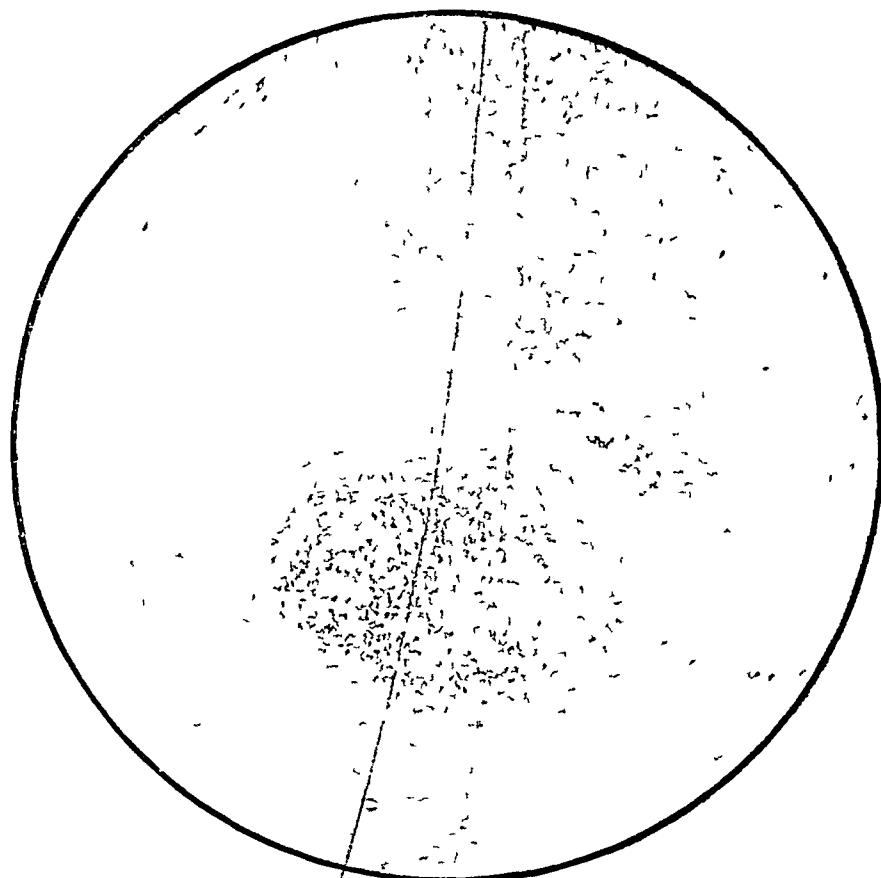


Fig. 5.—Stage III. Marked increase in fibrous connective tissue with surviving islets of lymphadenomatous tissue.

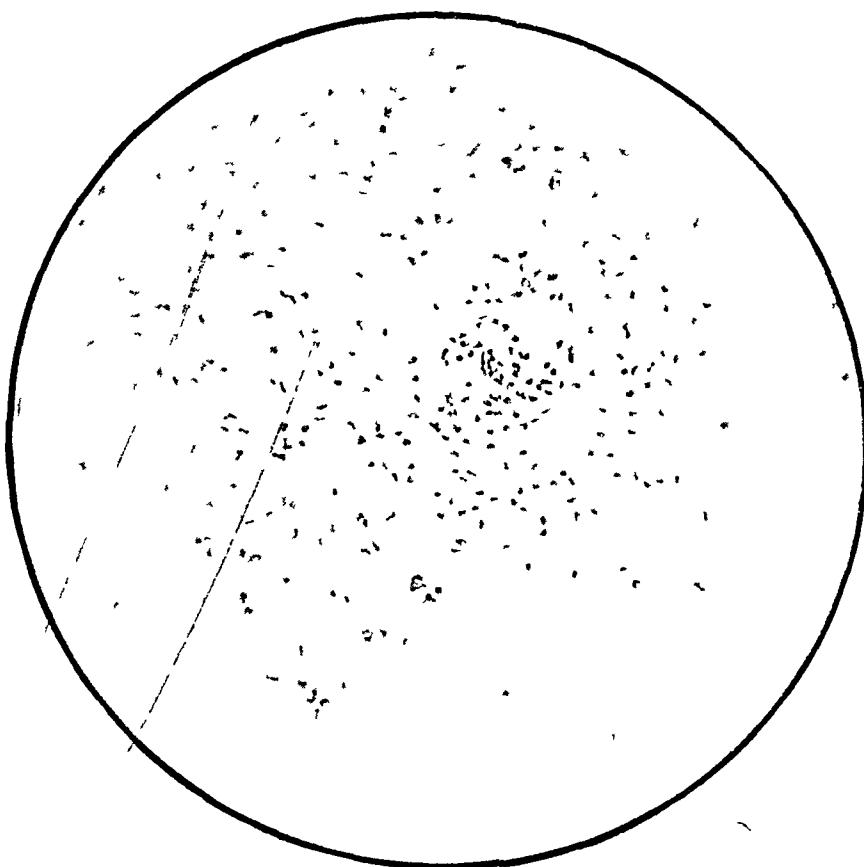


Fig. 6.—Stage IV. Scar tissue or fibrous connective tissue, poor in cells, few lymphocytes and one or two giant cells surviving.

the point of contention in stating that the disease picture is a peculiar chronic inflammatory process that in some cases no tubercle bacilli can be found and that in all the course differs from that of the ordinary glandular tuberculosis. Hence all are now agreed that whatever rôle the tubercle bacillus or its toxins may play in the pathogenesis of Hodgkin's disease the histological picture is one quite distinct from that of glandular tuberculosis. The supporters of the tuberculous etiology of this affection have gradually lost ground even in Germany. Ronzoni,<sup>9</sup> in a recent monograph on pseudolymphoma, admits that while tuberculosis is responsible for the majority of cases of granulomata of the lymph glands there are other toxins which may be at work. Very recently Hirschfeld,<sup>7</sup> at a meeting of the *Berliner hematologische Gesellschaft* spoke in no uncertain terms in favor of the entity of Hodgkin's disease (although objecting strongly to the nomenclature) and stated as his belief that it has nothing to do with tuberculosis. Benda and Wolf-Eisner still supported Steinberg's original contention.

In our particular case there was no evidence of tuberculosis in any organ during life, and the Calmette ophthalmic reaction was negative. We agree, however, with Wolf-Eisner in the unimportance of a negative ocular-tuberculin test in glandular tuberculosis. At autopsy the most careful and prejudiced search (for one of us was hopeful of establishing the tuberculous nature of the disease in this particular case) failed to reveal in the gross or microscopically in any of the viscera the slightest evidence of old or recent tubercles or acid-fast bacilli. Furthermore repeated cultural and inoculation tests both during life and after death, proved entirely negative. The giant cells in no way resembled those found in tuberculosis. The eosinophilic collections which may according to some observers, sometimes exist in glandular tuberculosis, are at all events very rare.

While a syphilitic infection was denied by the patient, the occurrence of an illegitimate pregnancy made us doubly careful in our search for therapeutic test in the shape of a long course of potassium iodid in full luetic stigmata though none such were found we applied the doses, during which time the glandular enlargement only continued to increase and the course progressed downward.

We believe, therefore that in our case we have clinical and pathological evidence that neither tuberculosis nor lues played a part in the pathogenesis of the disease. We must admit that, whatever be the nova that is responsible for the series of changes in this disease, it is as yet as

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<sup>9</sup> Ronzoni Abst in Folia haematol, 1909, vii

obscure as that of leucemia and pseudoleucemia. We agree, however, that the disease, both clinically and pathologically, is a peculiar chronic inflammatory process, as shown by the fever, sweats, moderate leucocytosis, secondary anemia, emaciation, the presence of endothelial proliferation and numerous eosinophils, the changes in the blood-vessels and the gradual fibrosis. This we believe to be best emphasized by the term "granuloma." But to differentiate this condition from the usual infectious granulomata as syphilis, tuberculosis, actinomycosis, etc., we would suggest the addition of some modifying adjective, as "cryptogeneticum." The term "granuloma malignum" of Benda and Hirschfeld we object to on account of the implied qualities of malignancy and tumor formation.

#### CONCLUSIONS

- 1 The belief of Fischer, Reed and Longcope in a clinical and pathological entity of the disease described by them is justified.
- 2 The process resembles a chronic inflammatory condition distinct from tuberculosis or syphilis.
- 3 That it would be wiser to exclude from the medical terminology of the future the name Hodgkin's disease as only serving to confuse and to create needless controversy.
- 4 That of all the proposed names for the process the most suitable one would seem to be "granuloma cryptogeneticum."

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# VARIOUS FORMS OF EXPERIMENTAL ARTERIAL DISEASE IN THE RABBIT

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Despite the fact that the experimental lesions in the rabbit's aorta occurring after the administration of adrenalin and other substances cannot be considered analogous to arteriosclerosis as seen in man, and despite also a reasonable doubt as to whether these lesions are really caused by such experimentation or are spontaneous in character, this study is of considerable importance in connection with the general problem of the degenerative and reparative processes in arteries. In the hope of adding somewhat to our knowledge of the subject and also of clearing up if possible, some of the doubtful points, I have studied during the past year the results of various forms of experimental injury. The methods employed include the administration of adrenalin and direct injury by crushing the vessel or applying an irritant such as silver nitrate. The suspension experiments of Klotz<sup>1</sup> have been repeated and, following the suggestion of an editorial writer in the *Journal of the American Medical Association*, based on recent investigations of loco-weed disease, the prolonged administration of barium by the mouth has been carried on, with the hope of thus explaining the spontaneous lesions. In all these experiments an equal number of animals have been used as controls and a careful study has been made of all animals used in other experiments in order to obtain information concerning the spontaneous occurrence of arterial disease.

As the general status of experimental arterial disease, including an excellent summary of the literature has recently been presented by Adler,<sup>2</sup> such will not here be considered.

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<sup>1</sup> From the Pathological Laboratory New York University and Bellevue Hospital Medical College, aided by a grant from the Rockefeller Institute of Medical Research.

1 Klotz, O. Arbeits-Arteriosklerose Experimentelle Centralbl f. allg. Path u. Anat., 1908, viii, 535

2 Editorial Barium, a Cause of Loco-weed Disease Jour Am Med Assn, 1908, li, 1338

3 Adler, I. Present Status of Experimental Arterial Disease Am Jour Med., Sc., 1908, xxvvi, 241

The question of spontaneous lesions may naturally be considered first. The significance of spontaneous lesions in connection with those produced experimentally was first seriously raised by Miles,<sup>4</sup> who reported spontaneous lesions in nearly 35 per cent of presumably normal animals and who suggested that the lesion assumed to be due to adrenalin might be truly spontaneous. This view has been opposed by Miller,<sup>5</sup> who summarizes the several large series of observations on normal animals without the discovery of spontaneous lesions, and by Pearce,<sup>6</sup> who found such lesions in but 6 per cent of the animals examined. It is of interest, in view of the possible influence of local conditions, that Miles' 35 per cent represents western rabbits, while Pearce's 6 per cent is based on New York and Massachusetts rabbits. Furthermore, it is of interest that, while Pearce found lesions in but 6 per cent of normal animals, lesions occurred with greater frequency in animals which had been in the laboratory for long periods of time and had been used for inoculation and other general experimental work. This latter observation suggests that a variety of influences may operate to produce these lesions in the rabbit.

#### SPONTANEOUS LESIONS

The animals examined for spontaneous lesions were those used in the class work of the departments of physiology and pharmacology, and for which I desire here to thank Professors Lusk and Wallace. These were presumably normal animals, used shortly after their arrival, in short-period experiments. In addition are included animals used in the department of pathology in various experimental studies.

The series comprises 210 rabbits. The aorta was examined from the aortic valve to the iliac bifurcation, and the iliac, carotid and subclavian branches followed for some distance. Of these animals thirty-one, or 15 per cent, exhibited arterial disease. In only one was the lesion as diffuse as in the adrenalin lesion, and in this animal only were lesions found below the diaphragm. This was a young rabbit, weighing 940 grams, in which the lesion appeared as a diffuse toughening of the thoracic and upper abdominal aorta. Four showed changes in the descending portion of the thoracic aorta and one a small pin-head-sized patch in the first part of the innominate artery, in all others the lesions were confined to the ascending and transverse portion of the arch of the aorta. The usual

<sup>4</sup> Miles, A. B. Spontaneous Arterial Degeneration in Rabbits. *Jour Am Med Assn*, 1907, *xlix*, 1173.

<sup>5</sup> Miller, J. L. Spontaneous Arterial Degeneration in Rabbits. *Jour Am Med Assn*, 1907, *xlix*, 1189.

<sup>6</sup> Pearce, R. M. Occurrence of Spontaneous Arterial Degeneration in the Rabbit. *Jour Am Med Assn* 1908 *li*, 1056.

lesion consisted of three or four irregular depressions just beyond the aortic valve.

Divided according to the purpose for which the animals were used, we have 117 rabbits utilized for class work in physiology and pharmacology with no previous treatment and 83 for experiments in pathology. The latter experiments included inoculation of sheep's blood for the Wassermann test and various injections in connection with a study of experimental nephritis. Of the former, sixteen or 13.5 per cent and of the latter fifteen or 18 per cent, showed lesions a somewhat greater incidence in animals kept for some time under laboratory conditions than in those used immediately. This difference is too slight to be seriously considered but is in keeping with Pearce's previous observation concerning the influence of experimental and laboratory conditions.

Of the above rabbits, fifty were bought in Chicago and are presumably representative of rabbits of the middle west. Seventy-six purchased from one New York dealer and represent animals raised in New Jersey; concerning the source of the remainder no definite information could be obtained. Of the fifty Chicago rabbits six or 12 per cent presented spontaneous lesions, of the seventy-six eastern, eight or 10.5 per cent. As far as these sources of supply are concerned there is, therefore little difference in the occurrence of spontaneous lesions.

These observations however, in connection with the available statistics of other investigators, demonstrate conclusively that the spontaneous lesions occur not infrequently. That the age of the animal is a factor is doubtful for five of the thirty-one animals in this series weighed less than 900 grams, two weighing 110 and 110 grams, respectively. Of these, the former presented the most extensive lesion found in the series. This is of interest in view of the fact that Pie and Bonnamouï<sup>7</sup> as well as Pearce and Stanton,<sup>8</sup> have called attention to the difficulty of producing adrenalin lesions in young (small) rabbits.

Histologically the spontaneous lesion cannot be distinguished from that due to adrenalin. The most prominent features are changes in the elastica and calcification. The elastic tissue loses its wavy appearance and the individual fibers become much thickened. Later these become calcified. Not infrequently a hyperplasia of the intima is seen—more frequently indeed, than is the case in the adrenalin lesion. This may

7 Pie, A., and Bonnamouï, S. Contribution à l'étude du déterminisme de l'athérome aortique expérimental. Compt rend Soc de biol, 1905, lviii, 219.

8 Pearce, R. M., and Stanton, E. M. Experimental Arteriosclerosis. Jour Exper Med, 1906, viii, 74.

possibly be due to the greater age of the spontaneous lesion Lesions of the type described by Ophuls<sup>9</sup> have not been found.

In connection with the study of these spontaneous lesions I have investigated the effect of barium administered by the mouth, thus adopting the suggestion of the editorial writer in the *Journal of the American Medical Association*, previously mentioned.<sup>2</sup> This writer calls attention to Crawford's study of the barium content of certain plants and the explanation of "loco-weed disease" as a poisoning by barium He then makes the suggestive observation, in view of the well-known effect of barium on the vascular system, that possibly the greater frequency of spontaneous arterial degeneration observed by Miles (35 per cent), as contrasted with Pearce's 6 per cent (New York), might be due to the forage plants of Colorado containing minute quantities of mineral poisons and, among others, possibly barium As this theory appeared very plausible, especially so in view of Miller's experiments with barium, I have attempted to produce a chronic barium intoxication by giving rabbits small doses of the chlorid with their food Four rabbits received barium chlorid by stomach-tube, daily, immediately after their feeding period. Three animals died after varying periods, but one received a total of eighty-six doses of half a milligram each during a period of fourteen weeks (February 1 to May 7) without the development of arterial lesions. Though small in number for definite conclusions, such experiments indicate that barium intoxication probably does not explain the spontaneous lesions

The production of arterial lesions by single injections of adrenalin has been rendered very doubtful by the recent observations concerning the frequency of spontaneous lesions Pearce and Baldauf,<sup>10</sup> in 1906, reported such lesions in each of a series of six rabbits receiving one-half to one and a half minims of adrenalin Unfortunately no control experiments were made At Dr. Pearce's suggestion I have repeated these experiments Two animals received, each, in divided doses, four minims of a 1 to 1,000 solution of adrenalin, and two were set aside as controls One of the former died after ten, and one after forty-one days No lesions were evident in either; the controls also showed no lesions It is evident that the previous positive results described by Pearce and Baldauf are in all probability to be explained by the occurrence of spontaneous

<sup>9</sup> Ophuls, W Spontaneous Arteriosclerosis of the Aorta (Atheroma) in a Rabbit *Jour Am Med Assn*, 1907, xlvi, 326

<sup>10</sup> Pearce, R M, and Baldauf, L K A Note on the Production of Vascular Lesions in the Rabbit by Single Injections of Adrenalin *Am Jour Med Sc*, 1906, cxxxii, 737

lesions Meyers,<sup>11</sup> working with a large number of animals, has reached a similar conclusion.

In other respects, unlooked-for results have been obtained with the use of adrenalin. Thus, in one group of four animals varying in weight from 1,500 to 2,000 grams and receiving, each, twenty-nine injections, over periods of fifty-two to one hundred and four days, the characteristic diffuse lesions of the experimental disease were found in only one. In an equal number of controls no lesions were found. As the total amount of adrenalin administered to these animals varied from 167 to 171 minimis, one must agree with other investigators that constant results do not always follow the administration of this substance. During the early periods of this treatment the animals failed to show the distress so characteristic of the intravenous injection of adrenalin and a fresh supply was used in the latter half of the injection. The use of an adrenalin altered by age, or otherwise deteriorated, cannot, therefore, be invoked as an explanation of the small percentage of positive results.

It is evident from the preceding discussion that the question of spontaneous versus experimental arterial degeneration is not a simple one—indeed, is one beset with many difficulties of interpretation, and, as Adler wisely concludes, demands a suspension of judgment until further investigation has cleared up the doubtful points.

#### DIRECT CHEMICAL AND MECHANICAL INJURY

For the purpose of comparing the lesions of the spontaneous and adrenalin disease with those of degeneration and repair following direct injury, the vessels in two series of animals were injured by chemical and mechanical means, respectively. For chemical injury, a 3 per cent solution of silver nitrate, as employed by Harvey<sup>12</sup> for the study of bone formation in arteries, was used. Laparotomy was done on three large rabbits and a silver solution was painted over a small portion of the abdominal aorta. The excess was removed after one minute by means of a sponge wet with salt solution. Of the three animals, two survived and were killed after forty-six days. In both the injured areas showed marked thickening of the adventitia. Histologically, the intima and inner portion of media were unaffected. In the outer portion of the media very definite calcification was present, and about this, involving especially the adventitia, was a great amount of fibrous thickening.

11 Meyers, M K. Die Wirkung von intravenosen Injektionen von Hypophysenextrakt und Brenzkatechin, sowie von einmaligen Adrenalininjektionen auf die Aorta von Kaninchen. Centralbl f allg Path u path Anat, 1909, xx, 109

12 Harvey, W H. Bone Formation in Rabbit's Aorta by Application of Irritant to Vessel Wall. Jour Med Research, 1907, xvii, 25

In another series the same portion of the aorta was crushed with an artery clamp, the jaws of which were covered with thin rubber tubing to prevent tearing. The pressure was applied for ten seconds. On removing the clamp, interstitial hemorrhage in the vessel wall could be seen, but no external bleeding occurred. Six large rabbits were so treated and killed after periods varying from fourteen to forty-seven days.

Macroscopically, the aorta appeared more opaque at the point crushed, but there was no appreciable thickening and no thrombosis. Microscopically, an atrophy of the connective tissue and smooth muscle of the media was seen, with stretching, straightening and rupture of the elastic fibers and marked hypertrophy of the intima. Despite the thickening of the intima, however, the vessel-wall was thinner at this point than elsewhere, owing to atrophy of the media. No calcification was seen. Although there is an interesting contrast between the results following the chemical and mechanical injury, the two lesions being of entirely different type, neither closely resembles the common lesion of the spontaneous or the adrenalin disease, though the repair following mechanical injury is an exaggerated form of that type of adrenalin injury in which intimal proliferation (Pearce) is occasionally seen.

For the purpose of still further studying the influence of the mechanical factor without employing toxins or causing direct injury, the recently published experiments of Klotz<sup>1</sup> were repeated.

Klotz describes the production of arterial lesions in rabbits as the result of suspending the animals daily by the hind legs for three minutes. This treatment was carried on for periods varying from ninety-two to one hundred and thirty days. He had demonstrated previously, by manometric studies, that by this procedure the pressure in the carotid and subclavian vessels could be raised. Thus he was reproducing a factor considered of prime importance in the etiology of human arteriosclerosis. The five rabbits subjected to this procedure showed more or less marked changes in the aorta, and the carotid and subclavian arteries. In the animal subjected to daily suspension for one hundred and thirty days there was found at autopsy a spindle-shaped aneurism of the thoracic aorta extending from the sixth rib to the diaphragm, a thickening of the wall of the aorta as far down as the renal artery, and a marked thickening of the carotid and subclavian arteries. It is of interest that, while the lesions in the aorta were of the adrenalin type, with primary change in the media, the peripheral vessels showed a primary thickening of the intima. As the arteries of the extremities by which the animals were suspended were free of lesion, it seemed justifiable to consider the

mechanical factor responsible for the arterial disease, especially as the negative controls appeared to rule out spontaneous lesions.

I have performed this experiment with two groups of animals. The rabbits chosen were all full-grown and in good condition. In the first experiment six animals were used, three subjected to suspension, three kept as controls. They were treated exactly as described by Klotz for a period of one hundred and thirty days, after which the animals were killed. Careful post-mortem examination of the aorta and its branches to the second or third division revealed no gross changes. Numerous sections were cut from different levels of the aorta and its branches and examined microscopically with negative results. Of the control animals, one showed most diffuse lesions in the ascending arch of the aorta.

I then decided to repeat the experiment, modifying Klotz's method by giving 100 cubic centimeters of water per stomach-tube, thirty to forty-five minutes before suspension, in the hope of increasing the vascular tension by the production of artificial plethora. In preliminary experiments it was found that this amount of water is absorbed within thirty to forty-five minutes after ingestion, and, allowing for the regulatory mechanism of diuresis, it seemed that at this period we would have the maximum temporary filling of the blood-vessels. The period of suspension was increased also to five minutes. Three animals were so treated daily for a period of a hundred days, but in no animal of the series could lesions of the arteries be demonstrated. I have no explanation to offer for these results, which differ so greatly from those obtained by Klotz.

#### SUMMARY

The occurrence of spontaneous arterial disease in the rabbit is an important factor in the experimental study of vascular disease, and a factor the status of which must be definitely determined before the results of experimentation along this line can be definitely accepted. In the course of this investigation 210 presumably normal animals were examined and spontaneous lesions found in 15 per cent. A slight but apparently negligible difference has been found in the incidence of these lesions in eastern and western rabbits and also in rabbits used immediately after purchase as compared with those passing through a long laboratory existence. The lesions occur in young (small) rabbits almost as frequently as in old rabbits. Histologically, the common type of spontaneous lesion cannot be distinguished from that due to adrenalin. Macroscopically, however, it differs from the diffuse lesion of adrenalin by being usually limited to a few foci occurring at the origin of the aorta. The peculiar spontaneous lesion described by Ophuls has not been

seen. The prolonged administration of barium by the mouth does not cause, as has been suggested, the appearance of spontaneous lesions. These spontaneous lesions apparently explain the results previously ascribed to single injections of adrenalin, for a repetition of the "single injection" experiments have given negative results. Likewise, in some groups of experiments, the long-continued administration of adrenalin in fairly large doses has led to the production of the diffuse lesion, considered characteristic of adrenalin, in a comparatively small percentage of animals.

Direct chemical injury, as painting the vessel with silver nitrate, causes a fibrous thickening of the adventitia and outer portion of media with calcification of the latter. Direct mechanical injury, as crushing by measured pressure with forceps, leads to atrophy of the media without calcification and to definite proliferation of the intima. The latter type resembles somewhat certain late stages of the adrenalin lesion with intimal proliferation, but neither can be considered analogous to either the spontaneous or adrenalin lesions.

Attempts to produce vascular lesions through increasing the blood-pressure by mechanical means, as in the suspension experiments of Klotz, have given negative results.

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## THREE CASES OF ADDISON'S DISEASE. ONE WITH ADRENAL TRANSPLANTATION

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It has been our privilege, during the present year, to see and study with others three cases of Addison's disease. Two were under observation at the Buffalo General Hospital, under the care of Drs Cary and Rochester, respectively. Dr Rochester's case was referred to him by Dr Kavuncoky. The third patient, a mulatto, was under the care of Dr Himmelsbach. The autopsy findings and blood-picture in another case of Dr Himmelsbach will also with his permission, be included.

Various points of difference and interest occurred in the symptomatology and history of these cases. One of them gave a typical picture of Addison's disease. The other two presented features which would tend to confuse the observer and increase the difficulty of diagnosis. In one of the cases we made an adrenal transplantation. All three cases terminated fatally, but the result of the transplantation experiment justifies a repetition of this procedure.

The points of interest may be best brought out by an epitome of the case histories followed by a brief analysis.

### REPORT OF CASES

**CASE 1—Patient**—A railroad switchman, native of the United States, aged 29, was admitted to the Buffalo General Hospital March 2, 1909, complaining of "yellow jaundice," kidney trouble, piles, scalp disease, sore throat. The family history was without interest, no tuberculosis or cancer. The patient has had three attacks of gonorrhea, the last four years ago. He had a chancre six years ago, does not recall having had mucous patches or skin eruption. He was under treatment at Hot Springs for one month. Wife has had two miscarriages, one at four and one at five months. No history of pulmonary trouble.

**Present Illness**—Chief complaint is that of weakness which has been progressing steadily during the last five months. This has increased more markedly during the past four days. Loss of appetite has not been marked until within the past week. Patient has always been of constipated habit but of late especially so, has had occasional vomiting spells which he ascribes to a nasal cataract. Vomiting bears no relation to meals. No cough. Patient has no well defined pain but complains of a dull ache low down across the back. His wife states that she first noticed a change in his color about seven months ago. Patient has difficulty in keeping warm.

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*Examination*—This showed a fairly well-nourished young man of medium height, with black hair, dark gray eyes and a dark skin of yellowish brown hue, not in itself remarkable. He had, however, a few freckle-like spots of a darker hue on the skin of his face and body, and numerous pigmented spots varying in diameter from 1 to 6 mm. There were also present more diffuse patches of pigment on the inner surface of the lips. The sclerotics were not pigmented and there was no evidence of jaundice. Physical examination of both chest and abdomen was negative, except that both heart sounds were weak. Both anterior and posterior cervical lymph-nodes were enlarged. Temperature on admission was slightly above normal, pulse 118, small in volume and of low tension, blood-pressure 90. The blood-pressure varied between 80 and 95, except on one occasion, when it reached 100, and just before death, when it fell to 50. On different occasions, in the order named, the Calmette, von Pirquet, and Moro reactions were tried. The first and last were positive. Ten days before death a positive Wassermann reaction was obtained. Blood examination showed the following hemoglobin, 90 per cent, erythrocytes, 4,200,000, leucocytes, 5,800. Differential count polymorphonuclears, 51 per cent, small lymphocytes, 33 per cent, large lymphocytes, 12 per cent, eosinophils, 2 per cent, basophils, 2 per cent. The urine showed evidence of chronic interstitial nephritis.

*Course of Disease*—The patient was admitted March 2 and died April 12. In view of the positive tuberculin reactions, tuberculin injections were administered, but without apparent benefit. Desiccated suprarenal was then administered by mouth in 30 cg doses t 1 d, but also without apparent benefit, although the patient's condition remained about stationary. After the positive Wassermann reaction and in view of the fact that there was a history of lues, it was suggested that antiluetic treatment be employed, with caution. This medication was administered in the form of protoiodid of mercury 2 mg t 1 d, beginning April 5. On the 8th (three days later) there was a sharp rise of temperature from 99 to 101.5 F, with salivation. The specific treatment was stopped and the patient put to bed. He grew very rapidly weaker and died on the morning of April 12, one week after the beginning of the antisyphilitic treatment.

*Autopsy*—The findings were, in brief, as follows. Some old pleural adhesions. Old pericardial adhesion. Flabby heart with thin muscle, fatty infiltration, atheroma around the coronaries. Lungs, nothing of interest (no tuberculosis). Liver somewhat cirrhotic. Retroperitoneal glands all enlarged, and some of them caseous. Mesenteric glands not enlarged. Both adrenals (right more than the left) caseous, broken down, and the right one in part a pus sac. Urinary bladder and bowels apparently normal. Brain apparently normal. Both kidneys capsule strips with some difficulty, cortex of normal thickness. Tubercl bacilli demonstrated in smears from both adrenals.

**CASE 2—Patient**—A mulatto, aged 56, hotel general utility man, had been ailing for two years, growing weaker and thinner, lost 30 pounds in weight, during the last four months before we saw him he had been turning darker, so much so that the increased pigmentation had been remarked on by his friends.

*Examination*—When he was first seen, in consultation with Dr. Himmelsbach, the patient was in bed because of nausea, vomiting and occasional epigastric pain. He was very nervous and was said at times to be demented. He complained also of vague pains in the limbs. The skin was uniformly dark, suggesting bronze, with areas of deeper pigmentation. There were patches of pigmentation on the buccal mucous membranes especially along the median line of the hard palate. On physical examination the chest and abdomen were negative. The heart sounds were strong, with accentuation of the second aortic sound over that of the pulmonic. The blood-pressure from May 1 to June 8 varied from 125 to 155 mm. There was moderate thickening of the radial artery. The urine examination gave

evidence of chronic interstitial nephritis. There was no edema. A positive von Pirquet reaction was obtained. Two blood examinations were made, with the following findings:

June 2 Hemoglobin, 90 per cent, erythrocytes, 5,230,000, leucocytes, 8,438  
Differential count Polymorphonuclears, 58.71 per cent, small lymphocytes, 32.38 per cent, large lymphocytes, 4.86 per cent, eosinophils, 4.05 per cent

June 13 Hemoglobin, 90 per cent, erythrocytes, 4,650,000, leucocytes, 10,000  
Differential count Polymorphonuclears, 60 per cent, small lymphocytes, 26 per cent, large lymphocytes, 10.5 per cent, eosinophils, 3.5 per cent

*Course of Disease.*—The patient became manic at the night of June 11, and was taken to the Buffalo General Hospital the following morning. On this day his blood-pressure fell to 95 mm., rising again to 105 the following day. He died in coma, June 14. The treatment was desiccated suprarenal, and finally adrenalin administered hypodermically.

*Autopsy.*—Both adrenals were found to be much enlarged. On section they were light brown in color and homogeneous in appearance except for caseous areas in each one 1.5 cm., the other 2 cm. in diameter. The mesenteric and retroperitoneal lymph nodes were not notably enlarged. Other abdominal organs apparently normal. Kidney capsules stripped with difficulty and the cortex was thin. Anatomical diagnosis: tuberculosis of adrenals, chronic interstitial nephritis.

*Case 3—Patient.*—A Russian Jew, aged 35, a tailor, was sent to Buffalo General Hospital by Dr. Kavmoki, on April 24. Family history has no bearing on the present illness. There is no history of tuberculosis or cancer. The patient had measles, never had any other disease. Three years ago, after a drink of whisky at a social gathering, he suffered from retention of urine, necessitating catheterization. At the same time it was noticed that the patient's skin became slightly pigmented. This pigmentation disappeared after a few days. No further trouble was experienced until ten weeks ago, when, at another social gathering, the patient drank two glasses of whisky and one of beer. He again suffered from retention of urine, and was relieved, by catheter, of 1,000 c.c. of normal urine. Since then his family have noticed increasing pigmentation of the skin. He feels weak and has no appetite. There is gastric disturbance after eating. Bowels move with help of Calisbad salts. He has nausea, but no vomiting, sleeps well, has no headache, but is dizzy. Patient has no night sweats, coughs and spits, feels cold.

*Examination.*—Temperature on admission to the hospital was 97.9 F., pulse 80, small and of low tension, but regular. Blood-pressure, systolic 88, diastolic 63. Tongue coated. Present weight, 135, greatest weight, 143 pounds. Observation of patient shows a man somewhat above medium height, slender, but not emaciated, with a somewhat anxious expression, brown eyes, dark brown hair and a dry dark skin. He looks like a dark-skinned Arab or Syrian. The skin of the whole body is thus uniformly darkened, with scattered blotches of somewhat deeper pigmentation on the face, and very deep pigmentation of the scrotum, penis, nipple areolæ, axillary and inguinal folds and waist and collar lines. There are also patches of pigmentation on the buccal mucous membranes, lips, cheeks and palate. There are likewise leucodermic areas in the skin of the back and scrotum, forming a striking contrast to the dark skin adjoining. Heart normal in size and shape, sounds feeble, pulmonic slightly accentuated over the aortic. Lungs poor expansion at both apices, right especially anteriorly, left especially posteriorly, no abnormality on auscultation. Blood-examinations were made on three occasions, as follows:

April 20 Hemoglobin, 74 per cent, erythrocytes, 4,044,000, leucocytes, 8,600  
Differential count Polymorphonuclears, 66.3 per cent, small lymphocytes, 19.3 per cent, large lymphocytes, 1.8 per cent, eosinophils, 6.8 per cent, basophils, 1.2 per cent, transitional, 4.3 per cent

May 7 Hemoglobin, 85-90 per cent, erythrocytes, 4,900,000, leucocytes, 10,300 Differential count Polymorphonuclears, 62.5 per cent, small lymphocytes, 17 per cent, large lymphocytes, 7 per cent, eosinophils, 13 per cent, basophils 0.5 per cent

May 16 Hemoglobin, 90 per cent, erythrocytes, 5,100,000, leucocytes, 12,850 Differential count. Polymorphonuclears, 47 per cent, small lymphocytes, 20 per cent, large lymphocytes, 12 per cent, eosinophils, 19 per cent, basophils, 2 per cent

No reaction was obtained from the Moro tuberculin ointment. The von Pirquet and Calmette tests were not used.

*Operation*.—The patient entered the hospital for the purpose of observation, and with his consent and desire, for a trial of adrenal transplantation. It was desired, if possible, to use a human gland for this purpose, but no available case presenting itself, and the patient's condition becoming alarming, it was decided to use the adrenal of one of the domestic animals. This was done on the afternoon of April 29, 1909. A female sheep, weighing 40 pounds, was killed by a blow on the head and immediately thereafter the left adrenal gland was removed per abdominal route. About one-fifth of the gland was shaved off, with a sharp razor, from each side, exposing the medulla. The ends were treated in the same way so that approximately two-thirds of the whole gland remained for transplantation and presented four raw surfaces for contact with the receiving organ. It was originally intended to use the kidney for this purpose, both because of its vascularity and because, in our animal experiments<sup>1</sup> we had made successful grafts into the kidney. The patient was, however, in such a precarious condition that it seemed almost certain that the attendant hemorrhage and shock, if the kidney were used, would prove immediately fatal. Therefore, the testicle, with much less favorable conditions for graft survival, was chosen instead. This was exposed, under local anesthesia, through an inguinal incision, the testicle being drawn up into the wound. An incision was made into the tunica albuginea. Just enough of the testicle proper was excised to allow of snug accommodation of the graft. This was buried and covered by the tunics, which were sutured together with 00 plain catgut.

*Postoperative History*.—At the first dressing, on the third day, the horse-hair skin sutures were removed. There was absolutely no sign of inflammatory reaction. In fact, the patient suffered practically no discomfort from the operation. Temperature and pulse remained normal. From the time that the patient entered the hospital much difficulty was experienced in getting him to take nourishment and in overcoming his extreme depression and discouragement. He was given, for a few days only, desiccated suprarenal. This was withdrawn because of ensuing nausea. Adrenalin by hypodermic was also employed, but given up shortly after the operation, to be resumed two or three days before death. For a time after the operation evident improvement in the patient's condition occurred. He became less despondent, ate better, felt somewhat stronger, and the vascular tonus increased. During this time, also, it seemed that the pigmentation somewhat lessened. Two or three days before death, weakness became suddenly more pronounced, the blood-pressure slowly fell, and the pigmentation deepened. Collapse occurred on the night of June 16 with a severe chill (as judged by the patient's shivering), followed by coma and death on June 17. The patient had lived two weeks and one-half after the adrenal transplantation. His death was, at least, not hastened by the operation, and we think it may have been delayed.

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<sup>1</sup> Am Jour Physiol, 1906 xv, No 5 Busch, F C, Leonard, T M and Wright, T. Further Results in Suprarenal Transplantation Jour Am Med Assn, 1908, li, 640

*Post mortem Examination of Transplanted Tissue*—Autopsy was refused, but the organ containing the graft was secured. On cross section of the testicle containing the graft, the latter was seen to be well imbedded in the testicular substance, distinguishable from it by difference in color and consistency. There was no macroscopic evidence of inflammation. At one end a number of new formed blood-vessels could be seen radiating from the graft into the surrounding testicle. The color of the graft and its general appearance were much the same as at the time of imbedding. On microscopic examination the adherence of the graft was still better shown. It was, in part, separated from the testicle by a band of new-formed connective tissue, with trabeculae penetrating the graft, and, in places, separating it into islands of adrenal tissue. A few scattered groups of cells presented the characteristics of adrenal medulla, in size, in arrangement and in staining properties. The major portion of the medulla had apparently become necrotic. A large part of the cortex, however, had survived, as represented by columns of smaller cells, readily staining with hematoxylin and eosin. Many new-formed blood vessels, containing normal (human) red blood corpuscles were found in the graft, entering it mainly by way of the connective tissue trabeculae. An interesting finding was the presence of numerous eosinophilic cells about the periphery of the graft and especially in the necrotic tissue.

In view of the microscopic findings and the length of time (two and one half weeks) after transplantation, we are justified in considering that a part of the graft had survived and was living at the time of the death of the patient.

**PARTIAL REPORT OF ADDITIONAL CASE**—The blood picture and autopsy findings in Dr Himmelsbach's other case, referred to in the first part of this article, were as follows:

**Blood**—Hemoglobin, 100 per cent, erythrocytes, 5,430,000, leucocytes, 12,600. Differential count Polymorphonucleais, 55 per cent, small and large lymphocytes, 38 per cent, eosinophils, 7 per cent.

**Autopsy**—Permission was obtained to open the abdomen only. Abdominal organs were normal except the kidneys, which were both caseous, the left entirely so and the right almost completely destroyed. Tubercle bacilli were demonstrated in smears from the adrenals and microscopic examination of sections showed typical tubercles with giant cells.

#### COMMENTS ON THE PRECEDING CASES

One of these cases presented the classic picture of Addison's disease. It could hardly have been mistaken for anything else. Unfortunately no autopsy was permitted, so that final proof was lacking.

It is evident from a careful analysis of these cases that no one symptom or sign or finding is pathognomonic. In two of the cases, in which blood-pressure records were frequently made, the blood-pressure was uniformly low, both heart and vessels being involved in the diminished tonus. In one of the low blood-pressure patients there was also a chronic interstitial nephritis of moderate degree. In one case, that of the mulatto, the blood-pressure remained high until just before death. In this case there was likewise a chronic interstitial nephritis of moderate severity, with some arterial thickening.

In one case there was a complicating history of syphilis and a positive Wassermann reaction. Because of this, antiluetic treatment was employed and undoubtedly hastened death. The intolerance for mercury in this instance was striking. We have since learned, in looking through the literature, that mercury is often poorly borne by these patients.

Three of the patients were pigmented in varying degree and showed pigmentation of the mucous membrane of the mouth. In one, the mulatto, the pigmentation might easily have been mistaken for the natural color of the negro.

Two patients gave positive tuberculin reactions. The third might also have given a positive reaction if more than one test had been used. The diagnosis was sufficiently clear without it.

The blood-picture in all was strikingly similar. There was no anemia. The hemoglobin percentage and red counts were both high. The fluidity of the blood was apparently diminished, which accounts, in part at least, for the high readings. The differential count is especially interesting. In all there was a decrease in the relative number of polymorphonuclear forms and an increase in the small and large lymphocytes, particularly the former. There was an increase in the number of eosinophiles from a moderate to a marked degree. In one case this was progressive, as was also the lymphocytosis. In this case, also, eosinophiles were found in numbers about the necrotic portion of the transplanted adrenal. What the significance of the eosinophilia is we do not know, or whether it has any significance. We are looking over our sections of transplanted adrenals in animals with this point in mind and are beginning an experimental study in animals.

On the therapeutic side there seems to have been little, if any, benefit from the use of adrenal, either of the whole gland by mouth or of its active principle by hypodermic injection. We still think that at present adrenal transplantation is the most promising method of therapy.

Our one transplantation in man was far from discouraging. In the first place, we had to be content with an organ for the reception of the graft which we felt was not the most suitable. In the second place, we were obliged to use the adrenal from another species of animal, instead of from another man as we had wished. In spite of these facts, a large part of the graft lived for two weeks and a half. Not enough survived to save the patient. Whether it might have become adapted to its new environment and functionated adequately had the patient been less far advanced in the disease, we cannot, of course, say.

Several attempts at adrenal grafting have been made, but none with as long survival of the patient and none with any demonstrable graft survival, so far as we know, besides ours.

We are at present carefully studying the literature of Addison's disease and expect, later, to be able to give a more detailed and accurate analysis.

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# THE TOTAL ENERGY REQUIREMENT IN DIABETES MELLITUS

BASED ON OBSERVATIONS WITH THE PETTENKOFER-VOIT CHAMBER

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Although the work on the various phases of metabolism in diabetes mellitus has become voluminous, there are but few records of the respiratory metabolism and of the total energy requirement. The statement commonly made in text-books and literature on the subject, that there is practically no change from the normal, is based almost entirely on the observations made in a severe case of diabetes by Pettenkofer and C. Voit<sup>1</sup> in 1867. In the original article no caloric estimations were made and incorrect conclusions were drawn, which were subsequently corrected by C. Voit<sup>2</sup> and F. Voit<sup>3</sup>. Graham Lusk,<sup>4</sup> using unpublished figures obtained from Erwin Voit, gives the caloric determination of the same case as 34 calories per kilo. None of these authors give the figures of the reckoning Ebstein,<sup>5</sup> in 1898, determined the twenty-four-hour carbon dioxide output in a case of severe diabetes, but did not go into the question of energy requirement. In his article he says that Lehman will consider the details in a later publication, but we have failed to find any such article or to find any reference to it in literature. Livierato<sup>6</sup> also made some tests in cases of diabetes, but his work has been considered so unsatisfactory that other investigators have refused to draw conclusions from it.

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<sup>1</sup> From the Laboratories of the II Medical Clinic, Kgl Charité, Berlin

<sup>1</sup> Pettenkofer and Voit Ueber den Stoffwechselverbrauch in der Zuckerkrankheit. Ztschr f Biol., 1867, III, 380

<sup>2</sup> Voit, C. Physiologie des Stoffwechsels, 1881, p. 328

<sup>3</sup> Voit, F. Ueber den Stoffwechsel bei Diabetes Mellitus. Ztschr f Biol., 1892, XXIV, 129

<sup>4</sup> Lusk, Graham Ztschr f Biol., 1890, XXVII, 478

<sup>5</sup> Ebstein Beitrag zum respiratorischen Gaswechsel bei der Zuckerkrankheit. Deutsch Med Wehnschr., 1898, XXIV, 101

<sup>6</sup> Livierato, P. E. Schwankungen der von Diabetiker ausgeschiedenen Kohlensäure. Arch f exper Path u Pharmakol., 1889, XXV, 161

Falta,<sup>7</sup> in a recent publication, gives the results of three cases of diabetes observed together with Benedict and Joslin in which an Atwater-Benedict chamber was used. He gives no details except a statement that two of the cases were severe, and that the metabolism was determined in a condition of hunger and with observations lasting six hours. His figures vary from 30 to 35 "Kal pro St", as this would mean about 785 calories in twenty-four hours, we imagine he means "Kal pro Kilo". Observations have been made with the Zuntz-Geppert apparatus by many workers—Leo,<sup>8</sup> Weintraud and Laves,<sup>9</sup> Nehring and Schmoll,<sup>10</sup> Robin and Binet,<sup>11</sup> Magnus-Levy,<sup>12</sup> and others. The Zuntz-Geppert apparatus, however, only determines the direct exchange of oxygen and carbon dioxide for short spaces of time—usually for ten or fifteen minutes in each of several consecutive hours. This gives much valuable information, particularly in regard to the utilization of various foodstuffs, but, on account of the short period of investigation and the large chances of technical error, it is impossible to make reliable deductions as to carbon dioxide output for twenty-four hours. This can be seen by comparing the figures of the various investigators above mentioned.

At the suggestion of Heri-Privat-Docent Dr Theodor Brugsch, to whom we wish to acknowledge our deep indebtedness for his valuable help and advice, we undertook a series of three observations with the Pettenkofer-Voit chamber, using the more modern methods of chemical analysis of food, feces and urine. Our object was to ascertain whether or not cases of diabetes mellitus show a variation from the normal in the total energy requirement and the twenty-four-hour carbon dioxide output. The first observation was on a normal individual weighing 70.1 kilos as a control, the second on a patient weighing 70.4 kilos, with severe diabetes, acidosis and large sugar excretion, and the third on a patient weighing 68 kilos, with mild diabetes. As all three were of nearly the same weight and stature, the questions of variation due to body surface and weight were minimized.

7 Falta Ueber das Respirationskalorimeter in Boston Wien klin Wehnschr, 1909, VIII, 565

8 Leo, H Ueber den respiratorischen Stoffwechsel beim Diabetes mellitus Ztschr f klin Med, 1891, XII, sup Heft, 101

9 Weintraud, W, and Laves, E Ueber den respiratorischen Stoffwechsel im Diabetes Mellitus Ztschr f physiol Chem, 1894, XII, 603

10 Nehring, O, and Schmoll, E Ueber den Einfluss der Kohlehydrate auf den Gaswechsel des Diabetikers Ztschr f klin Med, 1897, XXI, 59

11 Robin and Binet Exchanges respiratoires dans le diabète Arch gén de med, 1898, I, 283

12 Magnus-Levy Respirationsversuche an Diabetischen Menschen Ztschr f klin Med, 1905, lvi, 83

The Pettenkofer-Voit chamber was the one used and described by Steyrer,<sup>13</sup> and the methods, which were the same for all three cases, followed his very closely. First the chamber was tested by several normal candle burnings. Then, before each subject was put into the chamber, his nitrogen excretion was determined for several days in order to be able to give sufficient protein food to bring about an approximate nitrogen balance. Enough fat and carbohydrate were added to cover the probable caloric needs and water was allowed *ad libitum*. In each case the diet was practically the same as that which the subject had been having for the previous week. On the morning of the observation, after several hours of fasting, a meal was given and also a 0.3 gm carmine powder. Then the subject was put in the chamber for twenty-two hours, all reckonings being corrected for a twenty-four-hour basis. While the subject was in the chamber two more meals were given, the last one being at least five hours before the end of the observation. During practically the whole time the patient was in bed in a condition of *Zimmerruhe*, doing no kind of work except the movements of eating, reading and turning in bed. Three hours after leaving the chamber a meal was given, together with a second carmine powder.

The food given was made up in double quantities and divided equally in two portions by weight, one being given to the subject of the investigation and the other being analyzed. The feces were collected from the appearance of and including the first carmine powder, up to the appearance of the second. The specimen of urine was collected in the usual way during the twenty-four-hour period of the observation. Food and feces were dried over a water bath for six days and then for a short time in a drying oven at 60°. The amount of nitrogen was obtained by Kjeldahl's method and protein calculated by multiplying by 6.25 and protein carbon by multiplying by 3.28. A weighed portion of each, food and feces, was extracted with ether (feces method of Brugsch<sup>14</sup>) and the amount of fat obtained. Carbohydrate determinations were made in most cases by boiling with 2 per cent hydrochloric acid and alcohol and titrating the sugar, in some cases by subtracting the protein carbon and the fat carbon from total carbon. The carbon of the fat was obtained by elementary analysis and a portion of the food from which the fat had been extracted was burned, thus obtaining the total carbon present. Ash was obtained by Kjeldahl's method and the amount of carbon by elementary analysis.

<sup>13</sup> Steyrer Ueber den Stoff und Energieumsatz bei Fieber, u s w Ztschr f exper Path u Therap, 1907, iv, 720

<sup>14</sup> Brugsch Fett bestimmung in den Fazies Brugsch and Schittenhelm, Lehrbuch klinischer Untersuchungs methoden, 1908, p 576

Sugar was determined by Kumagawa's<sup>15</sup> modification of Pavy's method and acetone by the method of Huppert-Messinger.<sup>16</sup> Control analyses were made in all cases, in some instances by Dr E. B. Leech of Manchester, England. In determining the caloric values the following generally accepted factors of Rubner were used.

	Cal per gm		Cal per gm
Protein	4.1	Fat carbon	12.3
Carbohydrate	4.1	Alcohol	7.0
Fat	9.3		

#### DETAILS OF CASES

CASE 1—June 3 4, 1909, D, physician, aged 27, weight 70.1 kilos, normal. In the following tabular matter, units are grams, unless otherwise specified.

	Food			
Beefsteak	120.0	Sugar	.	30.0
Rice	100.0	Bread	.	200.0
Butter	150.0	Milk	.	1000.0
Weight dried				559.3

	Analysis			
Protein	81.3			
Fat	199.8	N	13.01	
Carbohydrate	251.4			C in fat
Ash	16.1	C	267.3	113.6
				C in carbohydrate and protein
				153.7

	Fats			
Weight dried				23.01

	Analysis			
Protein	7.9			
Fat	6.0	N	1.27	
Carbohydrate	4.01			
Ash	5.1	C	9.8	

	URINE			
Quantity				1600 cc
Albumin	negative	N	12.8	
Sugar	negative	C	10.50	C N 0.925
CO <sub>2</sub> output for twenty-four hours				783.8 gm
C output for twenty-four hours				213.77 gm

15 Kumagawa Salkowski's Festschrift, 1904, p 211

16 Huppert Messinger Brugsch and Schittenhelm, Lehrbuch klinischer Untersuchungsmethoden, 1908, p 510

	Food	Feces	Absorbed	Urine	Balance	Catabolized
Protein	810.3	7.9	73.4			80.0
Protein N		13.01	1.27	11.74	12.8	12.8
Protein C		42.67	4.16	38.51	-3.47	41.98
Protein calories						328.0
Fat	199.8	6.0	193.8			
Fat C	113.6	3.86	109.74		+36.64	73.10
Fat calories						899.1
Carbohydrates	251.4	4.01	247.39			247.39
Carbohydrate C (Disac.)		12.63		12.63		109.25
Carbohydrate C (Polysac.)	98.4	1.78	96.62			
Carbohydrate calories						1063.77

## SUMMARY

C of air	213.77
C of urine	10.56
	224.33
Less C of protein	41.98
	182.35
Less C of carbohydrate	109.25
C of fat catabolized	73.10
C of fat ingested	109.74
	109.74
C of fat retained	36.64
C of neg N balance	3.47
	3.47
Amount of C retained	33.17
	Calories
Protein	328.0
Fat	899.1
Carbohydrate	1063.77
	1063.77
Total	2294.87
Calories per kilo of body weight	32.7

CASE 2—June 10-11, 1909 S G, dental student, aged 23, weight 70.4 kilos, with severe diabetes. Two years ago it was found that the patient had diabetes mellitus with 2.5 per cent of sugar but no acidosis, the sugar disappearing from the urine on the withdrawal of carbohydrates from the diet. About six months before our observation he underwent two minor operations under chloroform anesthesia. Following the operation acetone and diacetic acid appeared in the urine, and the acidosis has been a constant factor since. The patient has been in the hospital for general treatment for about three weeks. On ordinary diet sugar amounts to 2 to 5 per cent, acetone trace. On a carbohydrate free diet sugar is present. Acetone and diacetic acid are present in small amounts, clearing up temporarily after a few oatmeal days. Hyperglycemia, 0.3 per cent. Heart and lungs normal. General condition of patient's nutrition and musculature good. No obesity.

	FOOD	
Chopped steak	150.0	Thin oatmeal gruel
Ham	49.0	Bread
Sausage	25.8	Soup (veg)
Bacon	12.5	Cognac
Butter	41.6	Coffee and tea
		3 cups

	Analysis				
Protein	68.25				
Fat	103.4	N	10.92		
Carbohydrate	55.53				
Ash	18.7	C	142.45	C in fat C in cognac C of carbohydrate and protein	74.62 7.33 60.5
		Feces			
Weight dried					37.56
		Analysis			
Protein			11.69		
Fat			14.8		
Carbohydrate			7.64 (by subtraction)	N	1.87
Ash			3.43	C	21.26
		Urine			
Quantity	3480 c.c.	N	17.21		
Albumin	negative	C	69.13	C N	4
Sp gr	103.5	Sugar			4% = 145
Beta-oxybutyric acid	"trace"				Acetone and diacetic acid, 0.0375
		Air			
CO <sub>2</sub> output for twenty four hours					748.8 gm
C output for twenty four hours					201.2 gm
		Food	Feces	Absorbed	Urine
Protein	68.25	11.69	56.56		—51.91
Protein N	10.92	1.87	9.05	17.24	—8.19
Protein C	35.82	6.13	29.69		
Protein calories					411.77
Fat	103.4	14.8	88.64		—123.29
Fat C	74.62	11.75	62.87		
Carbohydrates	55.53	7.64	47.89	145.0	—97.11
					Monosac
Carbohydrate C (Polysac)	21.68	3.38	21.30	58.0	—36.70
Carbohydrate calories					—308.15
Alcohol	14.06				14.06
Alcohol C	7.33			7.33	7.33
Alcohol calories					98.42

## SUMMARY

In reckoning the metabolism in this case the altered relations due to the excessive excretion of sugar must be taken into consideration. The amount of carbohydrate ingested was more than balanced by the amount excreted and is therefore not taken into the reckoning, since it was not available for energy. We find that 21.30 gm of carbon were ingested in the form of carbohydrates, while 58.0 were excreted, making the carbon of the negative carbohydrate balance

17 Several determinations of the beta oxybutyric acid were made with results showing a technical error. The amount in each case was very small, and we decided the error would be less in ignoring its presence than in using a mean of the determinations. The amount was so little that it would make but slight and unimportant changes in the final results.

36 70 This amount of carbon in the sugar must have been made up from the protein, and hence must be added to the carbon in the air, and the carbon of the non-carbohydrate part of the urine, in order to obtain the total amount of carbon in the metabolism of the protein, alcohol and fat

C of non-carbohydrate part of urine	11 13
C of sugar derived from protein	36 70
C of air	204 2
<hr/>	
Total C output	252 03
Less C of total protein	58 54
<hr/>	
	193 49
Less C of alcohol	7 33
<hr/>	
Total amount of fat C catabolized	186 16
C of fat ingested	62 87
<hr/>	
C from body fat	123 29
<hr/>	
Calories	
Protein	441 77
Alcohol	98 42
Fat	2289 76
<hr/>	
	2829 95
Carbohydrate	0 0
<hr/>	
From this must be deducted the heat loss of the sugar built up, as we have added above the carbon of sugar derived from body protein	
	2829 95
	376 17
<hr/>	
Total calories	2453 78
Calories per kilo of body weight	34 8

It will be noted that the diabetic patient excreted 4.4 gm more nitrogen than the normal individual Rubner<sup>18</sup> states that 28.5 per cent of this excess equaling 0.5 calory per kilo is not utilized and hence should be subtracted from the total, leaving the figure of 34.3

CASE 3—July 3-4, 1909 Max M, government official, aged 39, weight 68 kilos, with mild diabetes For several years patient has had a mild diabetes designated by his physician as "kidney diabetes" We personally had no opportunity to make protracted observations, but it is said there is always a small amount of sugar present in the urine varying from 0.5 to 1.5%, regardless of diet We regret not having been able to go more deeply into the pathogenesis and clinical aspects The urine averages about 2 liters daily, and patient, with but slight carbohydrate restriction, showed 0.52 per cent of sugar before the observation, on the only control sugar test made by us The patient's general health, condition of nutrition and development were good and he was able to do his work without the slightest difficulty He was not a patient in the Charité, but underwent the observation as a matter of courtesy to Dr Brugsch

## 14 TOTAL ENERGY REQUIREMENT IN DIABETES MELLITUS

	Food			
Meat	250.0	Bread		230.0
Milk	650.0	Butter		66.1
Vegetables	300.0	Coffee		600.0
Compote	100.0			

	Analysis			
Protein	111.25			
Fat	105.2	N	17.8	
Carbohydrates	190.20	C	233.49	C in fat 86.13 C in protein and carbohydrate 147.36

	Faeces			
Weight dried				29.1

	Analysis			
Protein	9.775			
Fat	6.585	N	1.58	
Carbohydrates	8.8	C	13.76	C in fat 5.185 C in protein and carbohydrate 8.485
Ash	3.81			

	Urine			
Quantity				1810 c.c.
Albumin	negative	N	9.17	
Acetone	negative	C	8.72	C N 0.96
Beta oxybutyric acid	negative	Sugn		0.4% = 7.76

## AIR

C <sub>0</sub> <sub>2</sub> output for twenty four hours			778.41 gm
C output for twenty four hours			212.3 gm

	Food	Faeces	Absorbed	Urine	Balance	Catabolized
Protein	111.25	9.875	101.375			52.62
Protein N	17.8	1.58	16.22	8.42	+7.8	8.42
Protein C	58.38	5.08	53.30			27.36
Protein calories						215.75
Fat	105.2	6.585	98.615		-27.136	
Fat C	86.13	5.185	80.915			108.08
Fat calories						1329.48
Carbohydrate	190.25	8.8	181.45	7.76		173.69
Carbohydrate C	88.98	3.4	85.58	3.7		82.48
Carbohydrate calories						712.13

## SUMMARY

C of non carbohydrate part of urine		5.62
C of air		212.3
		217.92
Less C of protein		27.36
		190.56
Less C of available carbohydrate		82.48
		108.08
C catabolized from fat		80.945
C of fat ingested		
C of fat from body		27.135

	Calories
Protein calories	215 75
Fat	1329 48
Carbohydrate	712 13
	<hr/>
	2257 36

Calories per kilo of body weight                    31 7

#### SUMMARY OF THE THREE CASES

	Weight	Total CO <sub>2</sub>	Calories	C per Kilo	CO <sub>2</sub> c c per kilo per min *
Normal	70 1	783 8	2295	32 7	3 95
Severe diabetes	70 4	748 8	2453	34 3	3 75
Mild diabetes	68 0	778 4	2258	31 7	4 04
Using factor CO <sub>2</sub> L					
	<hr/>	= 0 5091			
	CO <sub>2</sub> gm				

Comparing a number of cases by different observers of normal individuals of similar weight and under similar conditions, as given by Magnus-Levy,<sup>19</sup> it is seen that all three of our cases are close to the figures for normal individuals.

#### NORMAL INDIVIDUALS AT REST

Weight	Calories	C Per Kilo	Observer
64 8	1918	29 6	Siven
65 0	2136	32 9	Atwater
70 0	2279	32 5	Atwater
70 0	2278	32 5	Atwater
73 6	2101	28 9	Clopot
72 7	2269	31 2	Senden & T
73 3	2198	30 0	Ranke
Average			31 1

In neither the severe nor the mild case is there sufficient variation from the normal to warrant any statement of a decreased or increased energy requirement.

#### COMPARISON OF FIGURES OF VARIOUS OBSERVERS ON DIABETES

	Weight	Total CO <sub>2</sub>	Cal Per Kilo
P and V (severe)	54 0	621 0	ca 34
Ebstein (severe)	62 5	687 8	ca 36 †
Du B and V (severe)	70 4	778 4	34 5
Du B and V (mild)	68 0	778 4	31 7

\* Figures as given by Graham Lusk—no original reckoning

† Figures as given by Magnus-Levy—no original reckoning

In the case of Pettenkofer and Voit<sup>1</sup> we have selected the observation in which the food and conditions seem nearest to those of our case. The original investigations extended over a long period of time in which there

<sup>19</sup> Magnus Levy In Von Noorden's Handbuch der Pathologie des Stoffwechsels 1906, 1, 291

was a loss in weight, and so a slight difference will be found between our figures and some others published, such as Magnus-Levy's, in which a mean of five observations was taken. The different caloric estimations of different authors for Pettenkofer and Voit's work varies between 33 and 36 in the same case. Ebstein gives no original figures for the calories. It will be noted that all three of the severe cases are at the extreme upper limit of what is considered the normal metabolism.

The only method by which we can make a comparison with the Zuntz-Geppeit apparatus is by comparing the  $\text{CO}_2$  output in cubic centimeters per kilo per minute.

Our figures are as follows:

Normal	3.95
Severe diabetes	3.75
Mild diabetes	4.04

The average of twelve other cases of diabetes cited by Von Noorden<sup>20</sup> is 3.93, which is within the limits for a normal individual.

#### CONCLUSIONS

The total energy requirement of cases of diabetes does not vary from the normal. In addition to the 31-35 calories required for the normal individual at rest, the diabetic should be given enough extra calories to cover the loss of sugar in the urine. If this is not done there is a breaking down of the body protein and fat.

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20 Von Noorden Diabetes Mellitus Handbuch der Pathologie des Stoffwechsels, 1907, II, 46.

## SYPHILIS OF THE THYROID \*

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Gummata of the thyroid gland are so seldom discovered that it seems justifiable to review the literature on the subject while making this report. I shall, therefore, recapitulate as much of the data bearing on such lesions as it has been possible to gather, before proceeding to the discussion of the case in hand.

### PREVIOUSLY REPORTED CASES

Demme<sup>1</sup> (1879) reports three cases of syphilis of the thyroid in children in which gummatous nodules appeared in the thyroid glands concomitantly with syphilitic lesions of the viscera. He says that these gummata appear as grayish-red or grayish-yellow nodules, sharply rounded and, like malignant or tuberculous growths of these organs, destroy the parenchyma. The microscopic findings agree with those of gummata of the liver. In another place<sup>1</sup> he says:

In the course of congenital, hereditary syphilis, we find a few cases, and in my experience only in children, in which, accompanying syphilitic lesions of the viscera, we find gummatous nodules in the thyroids. They are sharply circumscribed, and present the same microscopic appearance as gummata of the liver.

Wagner<sup>2</sup> says that he has seen gummata of the thyroid, but gives no details. Büch-Hirschfeld<sup>3</sup> quotes Demme, saying that gummata may be found in the thyroids of the new-born and that he knows of a case in which gummata also occurred in the thymus, lung, liver and pancreas. Orth<sup>4</sup> also quotes Demme to the effect that gummata occur in the thyroid but rarely. Ziegler<sup>5</sup> says "Gummata of the thyroid are very rarely met

\* From the Pathological Laboratory of the University of Chicago.

1 Demme Krankheiten der Schilddrüsen, Bern, 1879, Gerhardt's Handbuch der Kinderkrankheiten, III, part 2, p 413, quoted from Clarke (Lancet, 1897, II, 389), Mendel (Med Klin., 1906, II, 833), and Fraenkel (Deutsch med Wehnschr., 1887, VIII, 1035).

2 Wagner Arch d Heilk., IV quoted from Fraenkel (Deutsch med Wehnschr., 1887, III, 1035).

3 Büch-Hirschfeld Lehrbuch der pathologischen Anatomie, Leipsic, 1882, I, 281.

4 Orth Lehrbuch der speciellen pathologischen Anatomie, Berlin 1887 I, 578.

5 Ziegler Text-book of Special Pathological Anatomy (transl by Macalister and Cattell from the 8th German edition), p 880.

with Naviatil<sup>6</sup> (1882) states that he has seen a gumma of the thyroid as large as the fist, but histological confirmation of this diagnosis is not given.

Fraenkel<sup>7</sup> (1887) reports the case of a woman 41 years of age who had syphilitic ulcers and gummata of the trachea and bronchi involving neighbouring lymph-glands. She died of the affection, which, post-mortem, was found to be widely disseminated, multiple gummata appearing in the liver, one in the right kidney, and syphilitic thickenings of the frontal bone and the tibia. The thyroids were not enlarged, but at the point where the isthmus joined the right lobe was a rather hard, yellowish-gray mass which was not sharply marked off from the neighboring parenchyma and was firmly attached to the trachea. It was 2.5 cm wide, 2 cm long and 1 cm thick. Histologically he found no giant cells but many round cells. The proliferating tissue confined itself to the inter-follicular regions and affected the parenchyma only by pressure. He found but little evidence of necrosis in this mass—fatty degeneration, caseation, vanishing of nuclei, etc.—such as one finds in even the smallest tubercle. The growth was not sharply marked off from the surrounding tissue, thus differing, as Fraenkel remarks, from tubercle and from the cases of syphilitic thyroids described by Denme. He demonstrated the Lustgarten bacillus in sections of the gumma (which makes one suspect tuberculosis). He thought these characteristic of syphilis.

Kohler<sup>8</sup> (1892) reports a case of a woman, 48 years of age, who had suffered in her youth from swelling of the glands of the neck but had never been really sick. At the time of examination she was married and the mother of two healthy children. She had a typical myxomatous swelling of the face, neck and hands. The trigonum colli mediale from the thyroid cartilage to the superior border of the manubrium was filled with a hard nodular tumor-like mass, which seemed microscopically to be of a fibrous nature. The thyroids were not palpable. There were no other symptoms suggestive of syphilis. Her husband had had an abscess in the groin some time previous. Iodid treatment cleared up all symptoms rapidly, the tumor vanished, the myxedema disappeared, the thyroids again became palpable. The diagnosis was made of gumma of the thyroid gland.

Pospelow<sup>9</sup> (1894) describes a case of myxedema occurring with diabetes insipidus, which was cured by antisyphilitic treatment, and con-

6 Naviatil Chin Beitr. Stuttgart 1882, pp 21-22 (Quoted from Wolfs Arch f klin Chin, 1883, xxix, 827)

7 Fraenkel Deutsch med Wehnschr, 1887, xxii, 1035

8 Kohler Beitr klin Wehnschr, 1892, xxix, 743

9 Pospelow Monatsh f prakt Dermat, 1894, vii, 125

sidered that in this case a syphilitic sclerosis of the thyroids was the cause of the cachexia. The patient had shown the characteristic primary and secondary lesions, and when the myxedema appeared had a gumma of the testicle and a gummatous swelling on the upper third of the left side of the larynx. The thyroids were also slightly enlarged and hardened.

Clarke<sup>10</sup> (1897) reports the case of a married woman, 38 years of age, who was seen Dec 28, 1896. About four years previously she had been treated for a gumma of the right arm which subsided under potassium iodid. She ceased taking medicine and soon three gummata appeared on the left side of the face and were similarly cured. About March, 1896, a gumma appeared at the front of the neck, and again potassium iodid was given, in September, 1896, the swelling began to ulcerate and she treated it by poulticing. She had been married thirteen years and had never been pregnant. No history of syphilis, aside from the gummata for which she had been treated, was obtainable either from herself or from her husband. A fortnight before admission to the hospital she noticed a difficulty in swallowing and could take no solids, her voice became a husky whisper, and breathing became difficult. She had occasional severe paroxysms of dyspnea, causing great distress. In the mid-line of the neck anteriorly was a hard cylindrical swelling, extending from the hyoid bone to the top of the sternum, so that the thyroid and cricoid cartilages could not be felt. The swelling rose and fell with deglutition. The upper part was ulcerated—a typical gummatous ulcer. Breathing became so difficult that on January 1 laryngo-tracheotomy was performed and a tube inserted. The relief was immediate. The gumma rapidly dwindled and sloughed off under potassium iodid. Microscopical examination showed a typical gumma, but no thyroid tissue. It was concluded that the whole thyroid had not been destroyed, because no myxedema appeared by June, 1897. A laryngoscopic examination made two days after the operation showed the following: epiglottis, right side of larynx, and right vocal cord, red but otherwise natural, left side of larynx so edematous that it projected as far as the middle line. The left vocal cord could not be seen. No ulceration was visible. The edema of the larynx subsided so that the tracheotomy tube was removed on January 7. Examination at that time showed that the left vocal cord had been almost destroyed, it being represented by a small nodule of tissue.

The next examples of gummata of the thyroid were reported by Mendel<sup>11</sup> (1906). In a preliminary discussion he suggests that some

10 Clarke Lancet London, 1897 II, 389

11 Mendel Med Klin, Berlin, 1906, II, 833

cases of supposed syphilis of the thyroid may simply be examples of "thyroiditis iodica." In support of this contention he quotes Seifert to the effect that in the secondary stage of syphilis the thyroids frequently undergo enlargement, but seldom to such an extent that they can be described as true cases of *stictuma syphilitica*. This enlargement occurs mostly in women, and only during the course of the antisyphilitic treatment, disappearing entirely in the course of a few years, apparently not being influenced in this process by the specific treatment. These Seifert considers to be cases of *thyroiditis iodica*. Mendel also gives a case of his own in which a girl, 16 years of age, in whom symptoms were rapidly disappearing under mercury, developed mercurial poisoning so that potassium iodid had to be substituted in the treatment. The thyroids immediately became swollen and hard, painful on pressure and swallowing. His diagnosis was *thyroiditis iodica*. He would class under the same heading the case of Wermann,<sup>12</sup> in which the swelling of the thyroids increased under iodin but decreased under mercury.

This class of cases becomes of considerable interest in view of the reports of a number of authors who are inclined to attribute such changes to *syphilis per se*, apparently never having considered the possibility of the *thyroiditis iodica* of Seifert.

E. Lang,<sup>13</sup> in 1851, noted that definite circumscribed nodules may occasionally be found in the thyroids in early syphilis.

Lanceieaux,<sup>14</sup> in his treatise on syphilis (1868), refers to a similar condition as follows:

A change in this gland is mentioned in several of the cases which form part of this work. A very manifest, and for the most part generalized increase of volume, a consistence more or less firm with yellowish color in places, such has been the aspect under which this organ has most frequently presented itself to the naked eye. The microscopical examination has revealed to us an increase in the number of glandular elements, together with a more or less complete fatty metamorphosis. We do not know of any case which gives evidence of a gummy deposit in the substance of this gland, but this is perhaps a consequence of the negligence with which post-mortem examinations are still too frequently made. The thyroid body is none the less frequently enlarged in women affected with syphilis of long standing.

#### Julien<sup>15</sup> remarks

The body of the thyroid generally escapes (syphilitic) affection, but it has been asserted on good authority that it once in a while presents a temporary swelling.

12 Wermann Beil klin Wehnschi, 1900, xxxvii, 122

13 Lang, E. Jahrest d Gesellsch f Natur u Heilk in Dresden, 1851 52  
(Quoted from Ziemssen Handbuch der specielle Pathologie und Therapie, Part I, iii, 337)

14 Lanceieaux Traité historique et pratique de la syphilis, 1868, 1, 377

15 Julien Traité pratique des maladies vénériennes, 1899, p 642

Mauriac<sup>16</sup> says

I have stated frequently that tumefaction of the thyroid gland is common in early syphilis. In one case which I have seen, there formed a veritable syphilitic goiter which lasted many weeks and became voluminous enough to cause compression of the trachea and the larynx, producing difficulty of respiration and hoarseness.

Engel-Reimers<sup>17</sup> reports a series of observations on 250 cases of syphilis. Of the 152 female patients, 86 had enlarged thyroids, while of the 98 male patients 44 had enlarged thyroids. The enlargement was confined to the lateral lobes, the isthmus not being involved. It was always a soft, painless swelling, which did not trouble the patients in the least, and in most cases would never have been observed excepting for the fact that it was searched for. "The swelling appears in the secondary incubation period or concomitantly with the first constitutional symptoms. It does not appear to be influenced by antisyphilitic treatment, but, like the swelling of the lymph-glands, disappears gradually in the course of a year or two." Engel-Reimers does not state the plan of treatment followed and apparently does not consider that the drugs administered could have been responsible in any way for the thyroid enlargements. He decides, however, that the habitual excitement of prostitutes cannot account for all the cases, although he thinks that such persistent overstimulation may cause such swellings to persist when they have once formed. He quotes Lancereaux to the effect that the body of the thyroid is frequently voluminous in women who are afflicted with syphilis of long standing.

Moritz Furst<sup>18</sup> reports the case of a child born with a goiter of considerable size, which he thought was undoubtedly due to syphilis. The father had suffered from this disease, and the mother underwent a course of mercurial treatment during her pregnancy, as she had already given birth to a still-born syphilitic child. Each lobe of the goiter was as large as a walnut. The swelling almost entirely disappeared spontaneously within six weeks of birth. No treatment was adopted.

The latest report which I have seen of swelling of the thyroids in early syphilis is that of Lockwood, who discusses a series of five cases. All of these patients were young women from 16 to 23 years of age. They had some enlargement of the thyroid simultaneously with the lymphatic enlargement, skin and mucous lesions of secondary syphilis. In one case the thyroid was said to be quite soft and uniformly enlarged.

16 Mauriac. *Syphilis primitive et syphilis secondaire*, 1890, p 474

17 Engel-Reimers. *Jahrb d Hamburg Statskrankenanst*, 1891-92, II, 430-436

18 Furst, Moritz. *Berl klin Wehnschr*, 1898, xxv, 1016

In this case all symptoms abated, together with the return of the thyroid to its usual size after a month's treatment with mercury. In no case did the swellings cause trouble.

Lockwood<sup>19</sup> says:

Since we have learned to look for this symptom it has been frequently observed. I have no doubt but that it is of the same nature as the enlargement of the lymphatic glands. This is known to be due to vascular engorgement. I have several times seen in the post-mortem room that this was so.

The coexistence of gonorrhœa and papillomata with the skin and mucous lesions seemed to have no bearing on the enlargement of the thyroids.

From a perusal of the above reports it will be seen that the changes in the thyroids in secondary syphilis may be considered, clinically, under two headings (1) cases in which the swelling is hard and more or less painful, and (2) those cases in which the swelling is soft and painless, causing the patient no discomfort. Whether or not these two groups of lesions arise from the same cause, or whether one is due to the iodin medication and the other to infection with syphilis must be decided by a fresh series of observations made with special reference to these points. From the reports of Seifert and Mendel, from the similarity in the time of appearance, lack of response to treatment, and general clinical course of these cases and those of other authors, there seems to be some ground for the suspicion that Seifert's diagnosis of thyroiditis iodica may be the correct one for at least the first group of cases, possibly for all. Whether or not the histological picture given by Lanceeaux is the correct one for all cases is also a subject for further research. This much seems to be settled that in early secondary syphilis the thyroid glands frequently become enlarged, that sometimes (we cannot say how often) this enlargement originates and progresses under potassium iodid, and that such swellings either disappear quite rapidly under mercury or fade away in the course of a year or two independently of specific treatment. The swelling may be hardly noticeable, or so marked as to cause dyspnea and hoarseness by pressure on the trachea and larynx. It may become hard and painful or remain soft and cause no trouble. In any case clinically, it is distinctly not of a gummatous nature.

But to return to Mendel's discussion of undoubted gummata. He first reports two cases described by Kuttner (1898—no references). The first of these was that of a woman, 39 years old, who, at 18, had had an exanthema and two years later a still-born child. On examination this woman was found to have a very hard thyroid as large as a small fist.

<sup>19</sup> Lockwood St Bartholomew's Hosp Rep, 1895, vii, 232

which interfered with breathing and caused a paralysis of the nervus recurrens. It was extirpated under the impression that it was a malignant growth, but examination showed it to be a gumma, as was also indicated by the results of iodid treatment for growths which developed later in other regions.

The second case was that of a man, 27 years old. His symptoms were similar to those in the preceding case. It was impossible to extirpate the growth, so that, after considerable difficulty, a tracheal cannula was inserted. A small piece cut from the new growth showed it to consist of sclerotic connective tissue with round-cell infiltration and characteristic proliferative processes in the vessels. The growth disappeared in three weeks under large doses of iodin.

Mendel then turns to three new cases. The first, from Professor Thiersch's clinic at Leipsic in 1883, is that of a woman, 38 years old. At the age of 12 she noticed a swelling in the neck which, in the last six months, had become greatly enlarged. It caused no pain. The swelling was the size of a child's head, situated on the right side of the middle line, and hard, irregular and nodular. There was great dyspnea. Tracheotomy was performed February 5 and extirpation February 8. Death from heart failure occurred February 10. Post-mortem examination disclosed amyloid spleen and numerous radiating scars and gummata in the liver. The extirpated tumor was 11 cm long, 10 cm broad and 9 cm thick. It was of an irregularly rounded form, varying in places from white to pale red to orange yellow in color. It was firm and dry, with the consistency of a rubber ball. The tumor included the whole of the right lobe of the thyroid. It presented, in section, radiating connective tissue strands extending from the periphery inward, with localized areas of round-cell infiltration. Near the periphery remnants of thyroid tissue could be found as scattered islets of cells and follicles with some colloid. An intermediate zone of spindle-shaped and Langhans giant cells could be differentiated. The center consisted simply of a structureless mass. The blood vessels of the two outer coats showed a typical syphilitic arteritis. The Langhans giant cells made Mendel suspect tuberculosis, but he was able by the absence of tubercle bacilli, the small amount of necrosis and the vascularity of the lesions to rule out such a possibility. His diagnosis was struma syphilitica.

In the second case (1892) the patient was a woman, 38 years of age, in good health and with two healthy children. In the left lobe of the thyroid was a hard, knotty body the size of a hen's egg. It was attached to the left side of the larynx and was connected to the isthmus of the thyroid by a hard band. Here its limits could not be definitely deter-

mined. The right lobe of the thyroid was somewhat enlarged, but had been so for years. The tumor had developed in three months. It was painless. A number of practicing physicians and surgeons had advised operation, since the hardness and swelling of the glands beneath the angle of the jaw suggested a malignant growth. After taking twenty grams of potassium iodid the tumor vanished and has never returned.

The third case (1905) was that of a woman, 63 years of age. She had had dysentery and erysipelas, had borne three healthy children, and had never aborted. In December, 1901, there developed in the left thyroid lobe, which was already enlarged somewhat, a hard tumor, which grew rapidly, causing difficulty in swallowing and breathing, and finally necessitating tracheotomy in May, 1905. The esophagus was so much involved that only fluids in small amounts could be swallowed. All physicians consulted diagnosed the case as incurable cancer. When seen by Mendel in August, the patient was almost moribund and, in spite of the tracheal tube suffered severe attacks of dyspnea and heart weakness, usually these attacks occurred at night. The neck had a circumference of 45 cm and presented a great tumor which reached from one angle of the jaw to the other. It surrounded the trachea and larynx and appeared to be firmly united with the vertebral column. It was hard, only a little roughened, caused no pain, and was not adherent to the skin. The glands of the neck were slightly swollen, but did not show the consistency of cancerous glands. There was no ulceration on the skin without, or on the walls of the food and air-passages within, no signs of metastasis. Combined mercury and potassium iodid treatment was instituted. Within three weeks the circumference of the neck decreased from 45 to 33 cm. The tracheal cannula was removed, the wound healed and by the beginning of September the woman was considered cured. About the middle of October a hard painful swelling appeared in the region of the left lobe of the thyroid. This developed rapidly, accompanied by a very sensitive swelling of the regional lymph-glands, causing great pain, and soon involving the left brachial plexus and practically all the structures in the neck. Death followed about the end of November.

Mendel believes that there was here, first, a struma syphilitica, followed, on healing, by a malignant tumor. He considers this a fresh demonstration of the malignant transformation of syphilitic scars in parenchymatous organs. He cites a case in which a gumma of the liver yielded readily to mercury, one year later a new tumor appeared in the liver which did not react to mercury and which operation proved to be made up of carcinomatous knots in the old syphilitic scars. Too many instances are known, however, of transient improvement under iodids,

of symptoms due to malignant growths, to make such improvement have much diagnostic significance, so that the nature of his third case must be considered as doubtful

Mendel makes the following summary of syphilis in the thyroid based on his own cases and such literature as was familiar to him

Besides the formation of circumscribed gummata, which appear concomitantly with visceral syphilis, there occurs a second form of syphilitic affection of the thyroids, which consists of an interstitial proliferation and leads to the formation of large, hard, markedly nodular tumors, which, by reason of their consistency, may be mistaken for malignant growths. They cause no pain but may lead to difficulty in breathing and swallowing. They develop, apparently, only in already diseased glands, and are more common in women than in men. Perhaps the iodin content of normal glands prevents the localization of the syphilitic virus in them.

Microscopically, *stroma syphilitica* presents an outer zone of connective tissue proliferation with degeneration of the parenchyma, and an inner zone of structureless material with infiltrating groups of round cells and numerous Langhans giant cells. The vessels show characteristic changes leading to necrosis and fibrous degeneration.

Clinically, it is necessary to differentiate only between gumma and malignant disease, since the course of the disease, the slight tendency to necrosis and the absence of tubercle bacilli serve to eliminate tuberculosis. The syphilitic tumor may be differentiated from carcinoma or sarcoma by the slow development, absolute painlessness, lack of adherence to overlying skin and the absence of metastasis. The reaction to potassium iodid and mercury clinch the diagnosis and should always, in doubtful cases, be resorted to before undertaking to operate.

*Thyroiditis interstitialis syphilitica* is probably more common than has been supposed hitherto, in most cases it has been considered a malignant tumor and either operated on or left alone, or as we might easily suppose, potassium iodid treatment has caused improvement before the real character of the lesion became manifest.

Thursfield<sup>20</sup> (1908) reported the case of a waiter, aged 53, who was seen Nov 4, 1907, complaining of a lump in his neck. He had first noticed the swelling one month previously. The patient had contracted syphilis about thirty years before and had been treated for six months. He had since had various tertiary manifestations which had been cured by potassium iodid. He had had repeated attacks of gonorrhea. The patient was a sickly-looking man. There was an oval swelling on the right side of the neck, measuring two inches by one inch, the long axis pointing obliquely outward and upward. The lower and inner end lay in the suprasternal notch, while the outer and upper extremity lay about an inch above the clavicle, but behind the posterior border of the sternomastoid muscle. The carotid artery lay behind and to the outer side. The skin over the tumor was natural. There was no difference in temperature on the two sides of the neck. The tumor was hard and solid with a smooth surface and rounded margin. It was painless and did not

<sup>20</sup> Thursfield Brit Med Jour 1908 1, 147

pulsate. It was adherent neither to the skin nor to the sternomastoid, but moved freely on swallowing and was clearly a part of the right lobe of the thyroid gland. The patient was ordered a mixture containing potassium iodid and ammonia carbonate. In a fortnight the swelling was reduced to half its size and in a month it could no longer be felt. The diagnosis was gumma of the thyroid.

The Museum of the Royal College of Surgeons of England contains a specimen of gummatus inflammation of the thyroid gland, which is described in the catalogue in the following words :<sup>21</sup>

Base of tongue, larynx and thyroid gland showing gummatus infiltration of the thyroid. The sternothyroid muscle is matted to the left lobe of the thyroid, which on section has a white fibrous appearance near the periphery, while the center more nearly resembles normal thyroid tissue. The upper end of the trachea is distinctly stenosed, and it, as well as the base of the tongue, shows the effect of past ulceration. Microscopic sections showed a fibrous tissue richly studded with nuclei. From a woman, about 60 who was brought into Guy's Hospital dead. There were gummata in the liver.

Richardson<sup>22</sup> quotes Abraham as having reported "three cases of women who developed exophthalmic goiter, the first five months after the primary lesion, the second during the height of the secondary infection, and the third two years after infection, all of whom were cured by antisiphilitic treatment." Richardson also says that Faisans and Audisterne "reported a case with both gonorrhœal and syphilitic infection, who developed a pseudomyœdema in which the myœdematous symptoms were not affected by mercurial treatment but disappeared under thyroid feeding." One can hardly accept this case as a definitely proved syphilitic affection of the thyroid. No statements are made regarding the presence or absence of changes in the size or consistency of the thyroid glands such as would be expected were the thyroid affection of a syphilitic nature.

Gombault<sup>23</sup> described a tumor-like growth which arose in the thyroid gland and spread to the neighbouring lymph-glands and connective tissue by continuity of tissue. It was adherent to the trachea. There was no history of chancre or mucous patches, but there had been an interstitial keratitis, and tibial periostoses were present. These latter findings were thought to represent late manifestations of hereditary syphilis. The age and sex of the patient was not given. There was no pulmonary tuberculosis. Histologically, the mass presented a caseous center surrounded by

21 Power and Murphy A System of Syphilis, 1908, II, 169

22 Richardson The Thyroid and Parathyroid Glands, 1905, ed 1, Phila 1905, J Blakiston & Co

23 Baith and Gombault Progrès Méd, 1884 VIII, 834

a thick wall of connective tissue in which were a large number of embryonic connective-tissue cells and a few giant cells. There was a marked arteritis obliterans. No typical tubercles were found. Repeated attempts to demonstrate tubercle bacilli by various staining methods failed. The lesion was diagnosed as syphilitic, and this diagnosis was concurred in by Cornil.

#### PRESENT CASE

The case which I have to report came to Dr H Gideon Wells for autopsy at the Cook County Hospital, Jan 19, 1909. The history was to the effect that the patient entered the Cook County Hospital, Jan 10, 1909, in the service of Dr Beck, complaining of hoarseness, great inspiratory dyspnea and pain on swallowing. The trouble had appeared four months previously, when the patient developed the above symptoms. This condition was constant and was subject to exacerbations at rather frequent intervals, in which the dyspnea was so great that the patient became cyanosed. Hoarseness was marked. There was history of syphilis five years previously, the patient had never suffered from any other serious illness. Examination of the larynx disclosed a paralysis of the adductor muscles. The neck was somewhat tender in the region of the thyroid cartilage, otherwise negative.

Tracheotomy was performed under local anesthesia, Jan 18, 1909, and a tube inserted with no relief to the patient, death followed about twelve hours later.

The autopsy disclosed the following lesions. Recent tracheotomy wounds, blood in trachea and bronchi, gummatous perichondritis of the right thyroid cartilage, with partial stenosis of the larynx, edema of the aryteno-epiglottidean fold, enlargement of the cervical lymph glands, gumma of the dura mater with old intracranial hemorrhage and compression of the right parietal and occipital lobes, chronic healing tuberculosis of the apices of both lungs, gummatous infiltration of the right lobe of the thyroid, and operative injury of the isthmus of the thyroid, left adhesive pleuritis, radiating atrophic scars in the skin of the forehead and penis.

The epiglottis showed no gross changes. The epiglottidean folds were swollen, especially the left, which was markedly edematous and had a gelatinous appearance. The orifice of the larynx was slit-like and the cords did not open as easily as normal. The edematous mucous membrane of the ventricles of the larynx filled up the entire ventricular space. There was connective tissue induration on the right side of the thyroid cartilage with thickening of the cartilage and adjacent tissues to about four centimeters. This included a solid tumor-like mass 2 cm thick on the outer side of the cartilage, composed of translucent but firm fibrous tissue, in the center of which was a more opaque white area. There was no ulceration in the larynx. The left vocal cord could be pushed away from the median line easily, while the right could not on account of a thickening on the inner surface of the thyroid cartilage similar to that on the outer surface, which reached to the median line. There was a thickening of tissue at the site of the right lobe of the thyroid gland. The gland was larger than normal, weighing 60 gm. The enlargement was uniform and diffuse. The posterior capsule was dense and translucent on the right side. The upper end of the right lobe was entirely replaced by diffuse, homogeneous fibrous tissue continuous with the perichondrial thickening. Deeper in the gland were found a few small, white nodules. The left lobe showed no changed areas but was slightly larger than normal.

Closer examination of the specimens preserved in Kaiserling's solution confirms the findings made at autopsy. The right lobe of the thyroid is about 7 cm in greatest length, 5 cm in width, and 2.5 cm in thickness. Its external surface

is fairly smooth. The cut surface shows an area 1.5 cm to 2 cm in diameter occupying the posterior medial portion of the upper pole of the gland. It presents an outer zone 3 mm to 5 mm in thickness, of a clear, homogeneous, semitransparent appearance, and a central area 7 mm to 10 mm in diameter, of an opaque, whitish material. The outer zone is continuous with connective tissue septa which run irregularly throughout the gland, dividing it into lobules of irregular size but of a somewhat oval shape. About 1 cm from the inferior extremity of the gland is another area of hyaline-like material, 5 mm to 7 mm in diameter. It, also, is continuous with quite heavy strands of connective tissue which radiate out into the gland. These septa converge with those from the upper pole at a thick-walled blood vessel 1.5 mm in cross section, situated about the middle of the anterior surface of the thyroid, forming there a third area of clear, homogeneous connective tissue with a markedly irregular outline.

Turning to the medial side of the right lobe we find that the tissue described in the posterior medial portion of the upper pole extends clear to the surface, and was apparently in very close apposition, if not directly continuous, with the perichondrial thickening of the right thyroid and cricoid cartilages.

The left lobe of the thyroid is 7 cm in length, 3.5 cm in width, and 3 cm in greatest thickness. About 1 cm from the tip of the inferior pole on the cut surface is a nodule 5 mm in diameter, which has the appearance of colloid. Above this and more anteriorly is a small spicule of whitish material with the consistency of cartilage. The left lobe is otherwise normal.

The growth on the right side of the larynx is triangular in outline, its base following a line from the superior tubercle of the thyroid cartilage to a point a little below the tip of the inferior cornu. The two sides of this triangle converge to a blunt point at the apex of the anterior arch of the cricoid cartilage. The distance from apex to base is 4 cm, while the base line has a length of 4 cm. The thickness of the growth gradually increases from the base to a point a short distance back of the apex, where it is equal to about 1 cm. The cut surface presents an appearance similar to that described for the largest nodule in the right lobe of the thyroid, namely, an outer zone of a translucent, hyaline material and an inner or central region of denser, more opaque, whitish tissue. It is directly opposed to the surface of the cartilages of the larynx, from which it can be rather easily peeled, leaving a smooth white surface.

The growth on the inner side of the cartilages shows no peculiarities not already brought out in the foregoing description.

For microscopical examination tissues were fixed in Zenker's fluid, and imbedded in celloidin. Sections were stained with hematoxylin and eosin.

Under the microscope, the left lobe of the thyroid appears to be poor in colloid but is otherwise normal. The right lobe shows a general increase in the perfollicular connective tissue, and in addition, a considerable area in which no thyroid cells can be made out. This area is, in the main, rather sharply marked off from the gland cells, but places are not difficult to find where no line of demarcation exists, the two tissues merging into each other. Thickened strands of perfollicular connective tissues are directly continuous with this new growth. The foreign tissue may be divided into an outer and an inner zone. The outer zone—that which borders on and sometimes infiltrates thyroid tissue—is roughly semi-circular in shape, is fairly thick, and consists to a considerable extent of large spindle-shaped cells lying in a myxomatous matrix. Occasionally a few large stellate and epithelioid cells are found and once in a while small groups of lymphoid cells occur. Several small atypical giant cells, containing three or four centrally placed nuclei, are present, as well as a few giant cells of the Langhans type. In many areas the proportion of matrix to cells is fairly large. The inner zone of this tissue, which is irregular in outline, consists of a network of fibrill like threads—necrotic material—in which an occasional large spindle, stellate or endothelial

like cell has become entangled. The contrast between these two areas is marked, though they shade over into each other at their line of contact. In some sections the spindle-celled and round-celled tissue assuming more of a round-celled type, can be seen to invade the interstitial tissue of bands of striated muscle. The process also appears to have invaded the periglandular fat tissue. In a few places one sees localized areas of connective tissue proliferation, composed of a central portion of epithelioid cells and a peripheral portion of lymphoid cells. These areas are small and occur in and near the margin of the region of foreign cells. Sometimes they consist entirely of round cells, which predominate largely in every case. Occasionally one of these areas possesses a necrotic center. In this lobe of the thyroid there is marked arteriosclerosis with calcification—a condition which is not present in the other lobe. The new tissue growth is quite vascular. All the vessels show marked proliferation and thickening of their walls, sometimes almost to the extent of total occlusion.

The chief effects on the thyroid tissue are apparently the results of pressure only, the proliferating tissue confining itself to the interfollicular regions.

The diagnosis is gumma of the thyroid gland, probably primary in the perichondrium of the cartilages of the larynx and secondarily invading the right thyroid body by direct contiguity of tissue.

#### SUMMARY

Twenty cases of gumma of the thyroid have been described. Eight of these—3 by Abraham, 2 by Mendel, 1 each by Kohler, Pospelow, and Thursfield—were diagnosed only clinically, without any definite anatomic proof of their syphilitic origin, 3 cases—2 of Mendel's and that of Clarke—were diagnosed both clinically and histologically, 8 cases—Demme's 3, the case in the Museum of the Royal College of Surgeons and 1 each by Barth and Gombault, Mendel, Fraenkel and Davis—were diagnosed histologically. Of the other cases, that of Navratal was probably diagnosed clinically—it is specifically stated that histological examination was not made. The basis for the diagnosis of Wagner's cases—number unknown—cannot be stated. It appears, then, that, as far as we can learn, this is the first case of tertiary syphilis of the thyroid gland—the diagnosis being confirmed by the anatomical findings—to be reported in American literature, the third reported in the English language, and the eleventh in the entire medical literature. These figures afford ample evidence of the great infrequency of definite syphilitic lesions in the thyroid.

In gummata of the thyroid the histological findings are identical with gummata in general. Clinically, as Mendel<sup>11</sup> has pointed out, the syphilitic tumor is almost painless, is not adherent to the overlying skin but may be firmly adherent to the trachea and larynx and even to the vertebral column, and does not produce metastasis. It usually is small, but may reach a large size. History of syphilis is suggestive, while the reaction to iodid of potassium and mercury is decisive for diagnosis. The growth may occur at any age. It may ulcerate, may cause severe dyspnea.

by pressure on the trachea and by inducing an edema of the larynx which may also seriously interfere with deglutition. It may cause hoarseness, it may cause myxedema by interference with the function of the thyroids, it may cause symptoms of exophthalmic goiter, and possibly the healed scar may undergo malignant transformation. Involvement of the nerve trunks in the neck may occur, with disturbance of their functions. The growth, if of small size, may produce no symptoms aside from the swelling. It frequently is not primary in the thyroids, but is secondary to a syphilitic perichondritis of the cartilages of the larynx.

Swelling of the thyroid occurs frequently in early secondary syphilis. The question as to whether or not this swelling is due to the syphilis or the treatment, or whether there may be two distinct types of thyroid enlargement in secondary syphilis, the one due to the syphilis, the other to the use of potassium iodid, is still open.

In conclusion, I wish to thank Dr. H. Gideon Wells for the opportunity to study this case and for his advice and assistance in the examination of the tissues.

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# THE PECULIARITIES OF NITROGENOUS METABOLISM IN PERNICOUS VOMITING OF PREGNANCY

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## THE CLINICAL PICTURE PRESENTED BY PERNICOUS VOMITING OF PREGNANCY

According to the classification of Williams,<sup>1</sup> pernicious vomiting of pregnancy may be of two types, one acute, the other chronic. In the acute form death may result within a relatively short period of time. The patient, who has been apparently a normal pregnant woman, suffering from what appeared to be the ordinary "morning sickness," suddenly begins to vomit all food. This symptom is soon followed by signs of prostration, unaccompanied by an increased pulse-rate or rise of temperature. After this condition has been maintained for a number of days considerable quantities of a coffee-ground-like material may be vomited at frequent intervals. The patient soon passes into a torpid state, leading to coma and resulting in death. This type of vomiting is not necessarily associated with great emaciation. The urine, which is apparently normal during the first days of pregnancy, later assumes an abnormal composition, since albumin, blood and various types of casts may be present. The temperature may or may not be significantly increased. In the last few days before death the conjunctivæ may present an icteric discoloration, or a decided icterus may be present, although its occurrence is rare.

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\* For the views expressed in the main portion of this paper F. P. Underhill is responsible. The clinical report has been rendered by Dr R. F. Rand. We desire to express our obligations to Dr Otto G. Ramsay, Professor of Obstetrics and Gynecology in the Yale Medical School, for his kindness in placing at our disposal the cases reported, which occurred in his service at the New Haven Hospital. We are also deeply indebted to Prof Lafayette B. Mendel for criticism of the manuscript and to Mr W. C. Rose, Assistant in Physiological Chemistry in the Sheffield Scientific School, for a large portion of the urinary analyses recorded.

<sup>1</sup> Williams, J. W. Pernicious Vomiting of Pregnancy, Abstract of Autopsy Protocol by H. T. Marshall, Johns Hopkins Hosp. Bull., 1906, xvii, 71.

Vomiting of the chronic type may continue over a very long period, during which extreme emaciation may occur, owing to the diminished intake or complete lack of food. The pulse-rate slowly increases, but fever is usually absent. Not until just before death does the dark vomitus characteristic of the acute type of vomiting appear. The patient is generally conscious until shortly before death.

#### THEORIES AS TO THE ETIOLOGY OF PERNICOUS VOMITING OF PREGNANCY

The presence of unknown toxic principles elaborated within the organism of the pregnant woman is supposed to be the underlying cause of pernicious vomiting. From a survey of the mass of literature relating to the subject, it is apparent that these hypothetical substances may originate from at least four sources namely, the gastro-enteric tract, the fetus, an ovarian secretion, and hepatic lesions. The foundation for the theory of the gastro-enteric origin of the toxic bodies was laid by Dirmoser,<sup>2</sup> who demonstrated an increased output of the products of intestinal putrefaction, indol derivatives etc., in the urine of women with pernicious vomiting. According to his view, the presence of these substances in the blood is sufficient to induce neurosis and vomiting results.

According to Veit<sup>3</sup> the fetal metabolic products finding their way into the maternal blood may cause certain cytolytic changes of a nature to produce lesions in the maternal organs and hemolysis of the blood. The ovary as a source of poisonous compounds is assumed to elaborate an abnormal secretion, or else the normal secretion may be suppressed.

The theory that hepatic lesions are responsible for the abnormal condition under discussion is based on numerous autopsy reports. According to the investigations of Stone<sup>4</sup> and Ewing,<sup>5</sup> the liver in these cases presents the lesions observed in acute yellow atrophy, the entire central portion of each lobule undergoes complete necrosis, while the periphery shows signs of fatty degeneration, and only a few cells remain perfectly normal. Some of the adherents of this theory, notably Ewing, maintain that pernicious vomiting, acute yellow atrophy and eclampsia are essentially one and the same disease.

#### THE COMPOSITION OF THE URINE IN PERNICOUS VOMITING OF PREGNANCY

The perfecting by Folin<sup>6</sup> of exact and relatively simple methods for the determination of the principal constituents of urine has made possi-

<sup>2</sup> Dirmoser, E. Ein weiterer Beitrag zur Autoantoxidationstheorie bei Hyperemesis gravidarum, Wien klin Wehnschr, 1903, xvi, 405

<sup>3</sup> Veit and Scholten Ztschi f Geburtsh u Gynak, 1903, viii, 210 (Cited from Williams)

<sup>4</sup> Stone Am Gynec, 1903, iii, 518

<sup>5</sup> Ewing Am Jour Obst, 1905, li, 145

<sup>6</sup> Folin Am Jour Physiol, 1905, viii, 45

ble the application of trustworthy methods to the field of pathological research on this secretion. The possibility of the demonstration of particular types of abnormal processes through a study of the urine has thus been greatly enhanced.

The first application of these newer methods to a study of the urine in pernicious vomiting was made by Stone.<sup>7</sup> As a result of his investigation the conclusion was drawn that in pernicious vomiting of pregnancy hepatic lesions pervert the metabolic processes in such a manner that various unoxidized nitrogenous compounds are eliminated instead of urea, which may in themselves exert a more or less toxic influence. The presence of leucin and tyrosin in the urine, together with a greatly diminished percentage of urea nitrogen and an augmented amino-acid-nitrogen ratio, was offered as proof of the correctness of Stone's conclusions. Only in fatal cases was the ammonia-nitrogen ratio disturbed.

Williams<sup>1</sup> selected the ammonia-nitrogen ratio as a means of diagnosis in pernicious vomiting, and on the basis of results derived from the determination of this urinary constituent, has divided vomiting of pregnancy into three classes, namely, (a) neurotic, (b) reflex, (c) toxemic. It is only in the last type that urinary analysis offers any evidence of noticeable metabolic disturbances. Here the characteristic feature to be observed in the urine is a marked decrease in the amount of nitrogen excreted as urea and a large increase of the nitrogen eliminated as ammonia. Indeed, the latter urinary compound may constitute about half of the total nitrogen excreted in the urine. Williams failed to detect acetone, diacetic acid, oxybutyric acid and allied substances, and in the urines of the two cases examined leucin and tyrosin were absent.

The research of Ewing and Wolf,<sup>8</sup> in which nearly all the nitrogenous constituents of the urine were estimated, led to the conclusion that in toxemic vomiting of pregnancy the chief features of urinary analysis are low urea, high amido or undetermined nitrogen, and usually high ammonia excretion. According to their view, emphasis should be given to the high undetermined nitrogen fraction as indicative of deficient desamination on the part of the hepatic cells, although they frankly admit that attempts to identify certain crystals obtained in the urine in their cases as leucin were unsuccessful.

<sup>7</sup> Stone Fetal Manifestations of the Toxemia of Pregnancy, *Med Record*, New York, 1905, lxxii, 295.

<sup>8</sup> Ewing and Wolf *Am Jour Obst*, 1907, lv, 289.

A COMPARISON OF THE URINARY PICTURES PRESENTED BY PERNICIOUS VOMITING AND INANITION

In pernicious vomiting of pregnancy the influence of inanition on the composition of the urine should be considered as a factor of paramount importance, since the two conditions many times exist together. If abstinence from food be continued sufficiently long the urine presents some striking similarities to that at times excreted in pernicious vomiting. In both pernicious vomiting and starvation the nitrogenous metabolism is generally somewhat decreased as indicated by the excreted nitrogen. There may be a diminution in the relative output of urea and an increase in the elimination of ammonia. The creatinin and uric-acid values apparently are not greatly deflected from the normal, or else show such irregularities that attempts to correlate them with the other urinary nitrogenous components have proved of little value. Acetone, diacetic acid and oxybutyric acid may be present in relatively large quantities in the urine of both pernicious vomiting and inanition, although, according to Williams,<sup>9</sup> "acetone, diacetic acid, oxybutyric acid and allied substances were not found in the urine" of patients with toxic vomiting. "The chief distinctions (between the urine in pernicious vomiting and inanition) are the inconstancy of acidosis, the occurrence of high total ammonia without acidosis and the high proportion of amido-acid nitrogen,"<sup>10</sup> all applying to pernicious vomiting. The observation of Stone that leucin and tyrosin are present in the urine of pernicious vomiting does not hold true for the urine in starvation.

SOME CONSIDERATIONS SUGGESTED FROM A REVIEW OF RECENT LITERATURE  
ON PERNICIOUS VOMITING

*Leucin and Tyrosin*—From a critical survey of the more recent literature relating to pernicious vomiting of pregnancy, several points of interest presented themselves. In the article by Stone<sup>7</sup> it is reported that leucin and tyrosin were recognized in the urine in several cases. From Case 1, Group A, the following figures are taken. For comparison, "normal" figures are also given:

	Stone	"Normal" (Folin <sup>11</sup> )
	%	%
Total N	6.2	6.1
Urea N	72.2	76.2
NH <sub>3</sub> N	1.2	4.2
Amino acid N	1.4	10.6

<sup>9</sup> Williams Johns Hopkins Hosp Bull, 1906, xvii, 79

<sup>10</sup> Ewing, James Acidosis and Associated Conditions III Clinical Types of Acidosis, THE ARCHIVES INT MED, 1908, 11, 485

<sup>11</sup> Folin, O Am Jour Physiol, 1905, xxii, 70

In this urine leucin and tyrosin were reported present. Yet from an inspection of the nitrogen partition just given, it is hard to conceive how so low a figure as 1.4 per cent of the total nitrogen will account for the undetermined nitrogen normally present in urine, which alone is usually much higher than this (see "normal" figures), and also for the nitrogen contained in the leucin and tyrosin, which were present in sufficient quantities to crystallize. In view of these figures, and from the fact that only the characteristic color and shape of the crystals obtained by the lead method are offered as evidence of the presence of leucin and tyrosin in these urines, it is apparent that the occurrence of these compounds in the urine of pernicious vomiting is not firmly established. One is still more unconvinced since these same substances were reported present in cases that were not serious. Furthermore, it is of interest to note the following, quoted from a paper published later by Ewing and Wolf:<sup>12</sup>

We have spent much time and labor in attempting to determine the presence and severity of toxemia by the abundance of crystals resembling leucin obtained by the lead method. Although we have been unable to identify these crystals as leucin, and think that in many cases they are chiefly urates, it is nevertheless true that they are extremely abundant in cases of acute yellow atrophy and eclampsia, and their numbers bear a close relation to the severity of the symptoms in nearly all cases of toxemia.

Until some evidence is offered more convincing than the above, however, the presence of leucin and tyrosin in the urine in pernicious vomiting of pregnancy cannot be said to have been established.

*Amino Acid Nitrogen*—In an article by Edgar<sup>13</sup> on the urine in pernicious vomiting are given the results obtained from a more complete determination of the urinary components. Comparison is also made of the urine in normal pregnancy. The undetermined nitrogen in non-toxic pregnancies varied between 8 and 18.5 per cent of the total nitrogen. On the other hand, in only one case of toxemic pregnancy is the percentage of undetermined nitrogen higher, and in this instance the difference is small. In the pre-eclamptic cases reported by Edgar there are only two instances in which the percentage of undetermined nitrogen exceeded that found by him for the normal pregnant woman. The ammonia nitrogen percentage was never high, nor was the urea lower than what might be possible for the normal urine. Since creatinin and uric-acid nitrogen figures were not uniformly given, it is assumed that the undetermined nitrogen was estimated by the Pfaundler<sup>14</sup> method. It is to-day well

12 Ewing and Wolf Am Jour Obst, 1907, IV, 312

13 Edgar, J C New York Med Jour, 1906, LXXXIII, 897

14 Pfaundler Ztschr f physiol Chem, 1900, XXX, 75

recognized that the Pfaundler procedure is of questionable<sup>15</sup> value as a means of estimating "amino-acid" or undetermined nitrogen in the urine. According to its author,<sup>14</sup> a portion of the creatinin and hippuric acid is to be included in this fraction. Even with due appreciation of the limitations of such a method, it is obvious that results obtained by it should not form the foundation for a diagnostic measure nor influence the obstetrician in his treatment of the disorder of pregnancy under discussion.

Ewing and Wolf employed the same method for undetermined nitrogen in a number of cases, and in these instances the conclusions which have been drawn are, therefore, not to be considered as firmly established. In a personal communication to one of us (Underhill) Dr Ewing has freely admitted the inaccuracy of the method, and has intimated that the results obtained by it must be interpreted with full knowledge of its inaccuracies. In the paper by Ewing and Wolf a relatively large number of apparent arithmetical errors may be noticed, which, however, Dr Ewing assures us, are mainly of typographical origin. Nevertheless, their presence interferes greatly with the interpretation of the data submitted, since one is uncertain whether a specific error is merely typographical, or whether the discrepancy remains unexplained. Aside from these apparent errors, however, there are a few instances in which criticism of the data given can be fairly applied. For example, in Case 8, partially reproduced in Table 1, on February 24 the sum of the various forms of nitrogen determined amounts to 98.6 per cent of the total nitrogen. The nitrogen contained in the form of creatinin and uric acid which was not included in the analysis of that day, would surely amount to more than 1.4 per cent, even though one takes for one's criterion Ewing and Wolf's own figures for these substances. In the same case, on March 1, the total nitrogen determined adds up to 100.9 per cent of the total nitrogen without any consideration of creatinin and uric-acid nitrogen. On the other hand, on July 29, only 75.65 per cent of the total nitrogen is accounted for, nor can it be assumed that the deficiency could be entirely eradicated by making allowance for the forms of nitrogen which were not estimated. These considerations enable one to realize how little dependence is to be placed on results for undetermined nitrogen obtained by the Pfaundler method. Even were it assumed that the figures for the undetermined nitrogen were accurate, it is difficult to understand how in Case 8, on February 24 or March 1, there is any evidence of deficient

<sup>15</sup> Folin, O. Am Jour Physiol., 1905, xiii, 93, where literature on the subject is given.

desamination, since on these days the sum of the percentages of urea nitrogen and ammonia nitrogen is 84.6 and 84.9, respectively, which is practically normal when compared with corresponding figures for total nitrogen in Folin's tables (See Table 1, in which comparative figures are given.) The same argument will apply with equal force to a case of toxemia of pregnancy published later by Ewing<sup>16</sup> (See Table 4.) In no single instance throughout the entire course of the observation is there any evidence of deficient desamination. The highest percentage of undetermined nitrogen attained was 22.7 but to this urine the following is appended "Uric acid uncertain." Referring again to Case 8, there is only one instance in which deficient desamination could be possible, that is, on July 29, when the sum of the urea nitrogen and ammonia nitrogen

TABLE 1—COMPARISON OF DATA FROM EWING AND WOLF FOR TOXEMIA OF PREGNANCY AND FROM FOLIN FOR NORMAL MEN

Case	Date	Total N Gm	Urea and Am- monia N %		Am- monia N %	Cre- atinin N %	Uric Acid N %	Undeter- mined N %
			Urea N %	Am- monia N %				
Case 8 *	2/24/05	6.24	84.6	72.2	12.4			14.0
Case 8	3/1/05	6.00	84.9	80.0	4.9			16.0
Case 8	7/29/05		68.41	63.1	5.31			7.24
Dr E v S <sup>†</sup>	1/30/	6.1	80.4	76.2	4.2	7.0	2.0	10.6
Dr Aug H <sup>‡</sup>	7/4/	5.9	81.7	76.0	5.7	8.0	1.6	8.7
Dr Aug H	7/6/	3.5	67.3	57.9	9.4	13.6	3.7	15.4

\* Ewing and Wolf Am Jour Obst, 1907, iv, 318

<sup>†</sup> Folin Am Jour Physiol, 1905, xiii, 70

<sup>‡</sup> Folin Am Jour Physiol, 1905, xiii, 70

amounted to only 68.41 per cent of the total nitrogen, but on this day the undetermined nitrogen was low. Dr Ewing, in his communication to us, has written as follows:

Granting that the 1905 cases (of which Case 8, just considered, was one) are not fully valid to-day, I must point out that the later cases in which we determined five substances offer evidence justifying the general conclusions of our studies.

In this we fail to agree with him, for in Case 7 (see Table 2), although on March 1 and March 3 1906 the undetermined nitrogen is high, we cannot see where deficient desamination can possibly play a rôle, since the sum of the urea nitrogen and ammonia nitrogen is as nearly the normal figure as is usually obtained for a comparable output of total

nitrogen (See Table 2, in which the percentages in Case 7 of Ewing and Wolf are compared with percentages taken from Folin's tables for comparable nitrogen excretion.) There are plenty of other instances in the work of Ewing and Wolf in which the same argument will hold, but the above example will suffice.

*Normal Urinary Standards*—It is the opinion of the writer of this portion of this paper that the principle of pronouncing any specific case of metabolism abnormal, merely from a consideration of the percentages of its nitrogenous constituents, is fundamentally incorrect and even though these ratios are compared with the so-called normal ratios for a given output of nitrogen, great caution should be observed in the interpretation of the results. Comparison of percentages with *normal* percentages, even when consideration is made of the total nitrogen output, carries with

TABLE 2—COMPARISON OF DATA FROM EWING AND WOLF FOR TOXEMIA OF PREGNANCY AND FROM FOLIN FOR NORMAL MEN

Case	Date	Total N Gm	Urea and Am- monia		Am- monia N %	Crea- tinin N %	Uric Acid N %	Undeter- mined N %
			N	%				
Case 7 *	3/ 1/06	12.5	85.2	71.0	14.2	1.1	0.9	12.6
Case 7	3/ 1/06	8.8	82.8	67.5	15.3	1.9	2.2	13.1
Case 7	3/ 5/06	9.1	89.6	78.2	11.1	2.2	1.6	6.6
Dr H B II †	3/16/	12.6	85.8	83.3	2.5	5.7	1.9	6.6
Dr E S A ‡	7/ 2/	8.6	84.0	77.7	6.3	5.0	0.8	10.2
Dr H B H §	7/21/	9.1	85.0	78.8	6.2	6.9	1.7	6.4

\* Ewing and Wolf Am Jour Obst., 1907, iv, 318

† Folin Am Jour Physiol., 1905, xiii, 108

‡ Folin Am Jour Physiol., 1905, xiii, 78

§ Folin Am Jour Physiol., 1905, xiii, 76

it certain assumptions, as, for instance, that every individual organism behaves in almost exactly the same fashion, a hypothesis that is manifestly incorrect. Furthermore, on this basis, it must be assumed that certain specific constituents of the urine are always normally eliminated in a fixed proportion to the total nitrogen. If we take ammonia as a specific example, the answer to this has been well expressed by Folin<sup>17</sup>

With pronounced diminution in the protein metabolism (as shown by the total nitrogen in the urine), there is usually, but not always, and therefore, not necessarily, a decrease, in the absolute quantity of ammonia eliminated. A pronounced reduction of the total nitrogen is, however, always accompanied by a relative increase in the ammonia nitrogen, provided that the food is not such as to yield an alkaline ash.

17 Folin, O Am Jour Physiol., 1905, viii, 92

In other words, the ammonia output does not necessarily bear a fixed relationship to the output of total nitrogen, nor is there a fixed standard for its elimination. Folin has also called particular attention to the variations which may be found in the output of ammonia nitrogen in different individuals, even when on essentially the same diet.

A good example of the fallacy of measuring any urine by a so-called normal standard, which is especially true from the standpoint of percentages, is shown in Table 3 for urea nitrogen and undetermined nitrogen. The figures<sup>18</sup> are taken from Folin's work.

It will be noted, first of all, that these analyses show the same output of total nitrogen (the diet was practically identical), and yet observe the absolute and percentage differences with regard to urea nitrogen and undetermined nitrogen. Is 66 per cent of the total nitrogen excreted as urea in the one case as against 79 per cent in the other to be considered as evidence of abnormality? Manifestly not, it merely illustrates the varia-

TABLE 3—UREA NITROGEN AND UNDETERMINED NITROGEN IN NORMAL SUBJECTS

Subject	Date	Total N Gm			Urea N Gm			NH <sub>3</sub> N Gm			Creatinin N Gm			Uric Acid N Gm			Undet N Gm			Urea N %			NH <sub>3</sub> N %			Creatinin N %			Uric Acid N %			Undet N %		
		E	S	A*	H	B	H <sub>1</sub>	7/4	5	3	4	2	0	40	0	40	0	08	0	19	79	7	76	87	3	7	6	14	3	7				
E H	7/18	5	3	3	5	3	5	0	47	0	47	0	58	0	09	0	63	66	4	9	0	75	4	11	6	17	11	9						

\* Folin Am Jour Physiol, 1905, xii, 78  
† Folin Am Jour Physiol, 1905, xiii, 76

tions which may occur in the metabolism of different individuals, even when on an identical diet. Again is the fact that in one case the undetermined nitrogen is three times greater than in the other to be taken as an indication of pathological processes, i.e., for instance as an evidence of deficient desamination? These differences are merely indications of the variation which may occur in normal metabolism, and they emphasize fully the need of caution in the interpretation of results obtained from analyses of the urine of persons in a diseased condition. Furthermore, a low urea nitrogen content, whether absolute or relative, is not sufficient evidence to indicate abnormality in intermediary processes, for instance, as indicative of suboxidation or deficient desamination. In any such

18 In the original table three arithmetical errors occur in the calculation of the percentages for urea nitrogen and undetermined nitrogen. On our calling Dr Folin's attention to these errors, he has given us permission to make the necessary corrections in this instance, and in an article on nitrogenous metabolism soon to be published by him, he will indicate certain other errors which have crept into the tables published by him in the American Journal of Physiology, 1905, viii, 45.

consideration of the urea nitrogen output the excretion of ammonia nitrogen must always be included, since the line of metabolism leading to urea formation is so intimately associated with the line leading to ammonia excretion that conclusions drawn from urea nitrogen elimination alone are extremely likely to be erroneous. Thus, if we compare the sum of urea nitrogen and ammonia nitrogen reported by Ewing and Wolf for "toxemia characterized chiefly by vomiting," with similar figures of Folin for approximately the same elimination of nitrogen, it will be observed that there is not a single instance in which there is as great a difference as was shown in the table above to be within normal limits. In other words, the ammonia nitrogen output fully compensated for any apparent lowering of the urea nitrogen output. Indeed, they conclude that "the chief feature of the urinary analyses (in toxemia of pregnancy) are low urea, high amido-nitrogen or undetermined nitrogen, and usually high ammonia excretion."<sup>19</sup>

Scrutiny of the results of another case,<sup>17</sup> partially reproduced in Table 4, reported by Ewing, reveals the same thing, namely, that according to the value of urea nitrogen plus ammonia nitrogen, there is no evidence of deficient desamination except on two days, July 18 and 29. On July 18, however, less than 83 per cent of the total nitrogen is accounted for, and the difference of July 29 is probably due to decomposition of the urine, since on this day the reaction was neutral.

The low urea in each instance is compensated for by the high ammonia. Comparing the figures for undetermined nitrogen in this table with some of those of Folin for approximately the same output of nitrogen, the greatest difference to be observed in the two sets of figures is a matter of a few hundredths of a gram of nitrogen, or 4 or 5 per cent. So far as the undetermined nitrogen is concerned in this table, we fail to see the least evidence of abnormal metabolism. Furthermore, there is no greater percentage difference between values for undetermined nitrogen given in any of the tables of Ewing and Wolf for pernicious vomiting and some of those for normal pregnancy than can be pointed out for normal urines.

The low creatinin figures given by Ewing and Wolf, and a part, at least, of the high undetermined nitrogen can be accounted for by the probable presence of significant quantities of creatin nitrogen which was not estimated. This appears likely from a later paper by Ewing<sup>18</sup> (see Table 4), and from our own results to be reported later, in which creatin nitrogen was generally present, especially when no food was ingested. A

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<sup>19</sup> Ewing and Wolf Am Jour Obst, 1907, Iv, 294

TABLE 4—URINARY ANALYSES IN A CASE OF TOXEMIA OF PREGNANCY

Date	Total N Gm	Gross Urea N Gm	Urea N %	—NH <sub>3</sub> N —		Creatinin N Gm	Creatinin N %	Uric Acid N Gm	Uric Acid N %	—Rest N — Gm	—Rest N %
				Gm	%						
6/11	3.58	2.77	77.5	1.82	50.9	0.95	26.6	0.11	3.1	0.12	3.4
6/18	2.11	1.57	64.4	0.99	40.6	0.58	23.8	0.19	7.8	0.08	3.3
6/20	3.33	2.43	72.8	1.77	53.1	0.656	19.7	0.265	8.0	0.023	0.7
6/21	3.34	2.41	72.2	1.79	53.6	0.62	18.5	0.266	8.0	0.024	0.7
6/22	3.69	2.84	76.5	2.31	62.7	0.53	13.8	0.28	7.6	0.04	1.1
6/23	3.33	2.56	77.0	2.47	74.2	0.09	2.8	0.21	6.4	0.06	1.9
6/24	2.75	2.17	75.0	2.17	75.0	0	0	0.193	7.0	0.045	1.7
6/25	3.38	2.64	78.3	2.13	62.5	0.51	15.8	0.167	5.0	0.12	3.6
6/26	2.58	2.03	78.7	1.75	67.8	0.28	10.9	0.184	7.1	0.03	1.2
6/29	1.28	0.77	59.9	0.354	27.8	0.42	32.1	0.17	13.3	0.043	3.4
6/30	1.05	2.86	70.6	0.71	17.5	2.15	53.1	0.33	8.1	0.06	1.6
7/ 1	1.45	3.63	81.5	0.49	11.0	3.14	70.5	0.223	5.0	0.05	1.2
7/ 2	1.81	1.50	82.9	0.16	8.9	1.34	74.0	0.079	4.4	0.026	1.4
7/ 3	3.13	2.73	81.3	0.30	8.7	2.48	72.8	0.157	4.6	0.011	0.3
7/ 8	2.66	2.06	77.5	0.14	5.3	1.92	72.2	0.167	6.3	0.034	1.3
7/11	1.50	3.30	73.3	0.255	5.7	3.04	67.7	0.318	7.1	0.085	1.9

portion of the undetermined nitrogen in their cases of "disturbed metabolism without symptoms" can perhaps in some cases be accounted for by the presence in the urine of significant quantities of hippuric acid. This would be very likely on a vegetarian diet. Again, although Folin has demonstrated that "the absolute quantity of undetermined nitrogen decreases under the influence of the starch and cream diet (jet) in per cent to the total nitrogen there is always an increase," his own tables show that this does not necessarily follow, when the nitrogen is decreased because of the administration of some other dietary. This is well shown<sup>20</sup> in Table 7 by comparing the figures for undetermined nitrogen on March 10 and April 1, here reproduced in Table 5.

Although on April 1 the total nitrogen output is less than one-half that of March 10, the absolute and relative quantity of undetermined nitrogen for April 1 is greater and compares favorably with some of the figures reported by Ewing and Wolf.

TABLE 5.—UNDETERMINED NITROGEN ON TWO SUCCESSIVE DATES

	Total N Gm	Undet N Gm	Undet N %
Mixed Vegetarian Diet, 3/10/—	17.0	0.68	4.5
Cereals and Bread Reduced, 4/1/—	6.7	0.88	13.2

Finally, the evidence furnished by the reports of Stone, Edgar, Ewing and Wolf fails to convince us that in pernicious vomiting of pregnancy urinary analysis reveals either suboxidation or deficient desamination in the organism.

In the foregoing considerations, we have attempted to show that percentage values alone may be of little value in the determination of whether a given urine is abnormal. A theory, like that of Williams, for instance, that when the ammonia nitrogen reaches 10 to 15 per cent of the total nitrogen, the patient is in grave danger, cannot be accepted as a diagnostic measure. Employment of such a theory as a working hypothesis in the treatment of pernicious vomiting will inevitably lead to erroneous conclusions. Not only must one consider the percentage value of urinary components, taking the total nitrogen output into account also, but of even greater significance is the *absolute* value of the different forms of nitrogen, and the normal, absolute and relative variations possible should receive due attention. No figures obtained in urinary analysis of this sort are of great significance unless due consideration has been given to the amount and character of the food ingested.

20 Folin, O. Am Jour Physiol, 1905, VIII, 108

We believe from the results thus far reported that urinary analysis gives no indication as to the cause of pernicious vomiting of pregnancy, and therefore cannot be regarded as a means of determining the patient's condition so far as this is connected with the disease itself.

#### A TENTATIVE THEORY TO ACCOUNT FOR THE COMPOSITION OF THE URINE IN PERNICIOUS VOMITING OF PREGNANCY

*Influence of Inanition on the Composition of the Urine*—From the data submitted by Williams and Ewing and Wolf, together with our own experience, the conclusion has been forced on us that in pernicious vomiting of pregnancy no significant change occurs in the composition of the urine so long as the patient is able to retain a sufficient quantity of nourishment. It is our conviction that the lack of food will suffice to account for the urinary picture presented, and although previous investigators have in a measure given consideration to inanition as a factor of importance, yet we believe that insufficient attention has been devoted to it. When comparison is made of the urinary findings in the two conditions, the similarity to be observed is most striking. Inanition tends to change the absolute as well as the relative quantities of urea nitrogen and ammonia nitrogen, and we have failed to discover in the cases of pernicious vomiting reported by previous investigators any more significant perversion than this. The existence of deficient desamidation, as indicated by the high undetermined nitrogen, and emphasized by Ewing and Wolf, has not been firmly established, and can be accounted for in part by the employment in its estimation of an inaccurate method, in part by the non-consideration of creatin and hippuric acid, and by the fact that the existence of this perversion is apparent rather than real, since too great reliance has been laid on the so-called normal ratios without due consideration of normal variations.

Ewing, who is the exponent of the deficient desamidation theory, inclines strongly to the view that the urinary findings presented by patients in simple inanition and in the pernicious vomiting are quite distinct. Nevertheless, he is able to enumerate only three differences, which have already been quoted in another part of this paper. The three distinctions indicated are high undetermined nitrogen in the urine of pernicious vomiting, which does not obtain for the urine of inanition, the inconstancy of acidosis, and the occurrence of high total ammonia without acidosis. The existence of the first-named factor, high undetermined nitrogen, has not in our opinion been established, as the previous discussion has indicated. It is presumed that by the term "acidosis" the presence of the acetone compounds is meant in Ewing's article. Little

comment is necessary on this, inasmuch as at best its significance is slight, and its appearance in the urine is governed entirely by the character of the food intake. From the excellent review by Ewing of the literature on acidosis (acetone, etc.), it is apparent that this condition arises only in the absence of sufficient carbohydrate supply in the body. Since no careful supervision of the dietary was reported in the cases of Ewing and Wolf, its appearance, or absence, should not be emphasized in indicating differences between the two types of urine.

The third factor, the occurrence of high total ammonia without acidosis, is worthy of careful consideration. In the first place, there are very few instances in the paper of Ewing and Wolf in which the ammonia is especially high, and in these cases there was noted the appearance of acetone bodies. Moreover, the observation that acetone bodies are absent is no proof that acidosis may not exist, that the high ammonia may not be united with some other perhaps hitherto unconsidered acid, or acids, which may be present in the urine of both simple inanition and in that of pernicious vomiting. Indeed, one of us<sup>21</sup> has already shown that paralactic acid in significant quantities may be isolated from the urine in pernicious vomiting, and in some unpublished experiments on prolonged starvation in man and in animals a zinc salt possessing the properties and chemical characteristics of lactic acid has been obtained from the urine. The observation that lactic acid may occur in the urine in both inanition and pernicious vomiting, presumably in combination with ammonia, appears to us to afford evidence that the origin of the lactic acid in the two cases is identical, namely, arising as a result of inanition, and this may carry with it the assumption that a part of the ammonia, at least in the two cases, is formed from identical processes. In other words, there is much to indicate that the high ammonia in pernicious vomiting arises, not as a result of pathological changes in organs induced by this condition, but as a result of processes initiated by starvation. We could also call attention to the possibility that hitherto little-considered acids, of which lactic is one, may be sufficient to account for high ammonia content, both in starvation and in pernicious vomiting.

*Theoretical Considerations*.—Our explanation for the urine picture observed in pernicious vomiting is that inanition is the factor responsible for the significant changes, i.e., the low urea and high ammonia nitrogen. As has been shown above, we fail to find evidence of any other changes which can be regarded as established, or which can not be accounted for. So long as it is a possibility for the patient to retain a suffi-

<sup>21</sup> Underhill, Jour. Biol. Chem., 1907, 11, 485.

cient food-supply, no perversions of the urinary components occur. Furthermore, when the ability to consume food is re-established, the unusual urinary finding is soon readjusted. Changed relations in the output of the nitrogenous constituents of the urine may not be apparent for several days subsequent to abstinence from all food. While it is true that a few days' fasting may be followed by the appearance of significant quantities of acetone bodies in the urine, i.e., acidosis, this phenomenon does not always accompany inanition of short duration. This is to be explained on the assumption that so long as the organism retains stored carbohydrate material a urine normal in its nitrogenous composition may be excreted irrespective of the fat content of the body. Although it is probable that the acetone bodies are derived from fat metabolism, their appearance in the urine is facilitated by the absence of adequate carbohydrate-supply in the body. In inanition energy is required to maintain the physiological efficiency, and this need is preferably supplied from stored carbohydrate, therefore, in the absence of this material, fat is drawn on. In the absence of carbohydrate, however, adipose tissue is difficult of combustion, but will yield a certain amount of the requisite energy. Besides the need of energy another nutritional necessity is the maintenance of the sugar content of the blood, which, in all probability, fat cannot readily yield. The protein material may then be drawn on to furnish the carbohydrate and, incidentally, a portion of the energy. This is accomplished by the demolition of the protein molecule, the assimilation of the carbon moiety and the simultaneous cleavage of the nitrogenous portion into substances readily eliminated. In the demolition of the protein molecule lactic acid arises, the presence of which in the blood is the signal for the body to reestablish its normal reaction, which is accomplished by intercepting ammonia salts on their way to undergo a transformation into urea. Such a process will account for a portion of the high ammonia nitrogen in the urine in both pernicious vomiting and inanition. The possibility that other acids having a similar origin may also be present is not excluded. The carbohydrate store of the body is not immediately depleted, but may be accomplished only after several days. According to this view carbohydrate-supply in the organism determines in large measure the occurrence of acidosis, i.e., high ammonia content in the urine. As soon, however, as the protein of the body is drawn on to furnish carbohydrate, acidosis makes its appearance. This explains the difficulty of inducing acidosis in dogs by inanition alone. The dog, as is well recognized, is capable of maintaining a glycogen store over an extended period. So long as glycogen is present in the tissues of this animal, there is no evidence of acidosis, but if glycogen is made to disappear by the admin-

istration of phlorhizin acidosis occurs<sup>22</sup>. It is not assumed, however, that fat metabolism is without influence in the production of acidosis. Indeed, in all probability, the combustion of adipose tissue may be assumed to be responsible for a large portion of the observed acidosis, especially in persons with much adipose tissue, but it is probable that this type of acidosis is also much more pronounced in the absence of sufficient carbohydrate. In emaciated individuals, however, it cannot be assumed to play such a prominent rôle. We would lay emphasis on the attempt of the body to obtain the requisite energy from protein as a source of acidosis (high ammonia) in lean individuals. In this attitude we differ from the work of Scholten and the theory of Wolf<sup>23</sup>. According to the latter, acidosis occurs only in fatty subjects, and a subject starved even to emaciation does not give evidence of acidosis. This statement emanates from the work of Brugsch<sup>24</sup>. His subject, according to Wolf, "had received no nourishment for forty days." In the original article, the facts are stated as follows.

"Seit Anfang November hatte sie sich von 1/2 liter dünner Milch pro Tag und 5 Eier in der Woche ernährt, die letzten 9 Tage vor ihrer Aufnahme hatte sie überhaupt nichts mehr hinunterbringen können, nicht einen Schluck Wasser." Although this diet might well lead to emaciation, it is possible that it was sufficient to prevent decomposition of tissue protein to an extent necessitating an increased ammonia output. The period of actual starvation was only nine days, which would not necessarily produce depletion of carbohydrate store in a woman of such small body weight.

On the other hand, if the urinary findings are the direct outcome of the pathologic condition itself in the acute cases in which starvation has not become a prominent factor, the urinary ratios should be markedly distorted. In the cases reported so little attention has been paid to the influence of diet that one is unable to render a satisfactory decision as to the specific influence the pathologic condition itself may have on the urine. In our personal experience, we have never seen a case of pernicious vomiting in which any of the nitrogen ratios were distorted so long as a reasonable quantity of food was retained. The mere statement that "the stomach retained almost nothing" is extremely indefinite. If our explanation of the significance of the reported perversions of the urinary constituents in pernicious vomiting is correct, the administration of carbohydrate-supply in these cases should be followed by a readjustment of

22 Marum Beitr z chem Physiol, 1907, 1, 105

23 Wolf New York Med Jour, 1906, LXXXIII, 813

24 Brugsch Ztschi f exper Path and Therap 1905, 1, 419

the distorted nitrogenous values without necessarily influencing the vomiting. On the other hand, if the cause underlying the inception of the vomiting is responsible for the urinary changes, supplying carbohydrate to the body should be without influence on the urine picture.

*Experimental Results*.—In the following pages are given the results of an attempt to test the tenability of the hypothesis advanced above. The reports here submitted are not offered as positive proof of the correctness of our theory, but the outcome in these cases has been so encouraging that the data are given in order that others, whose opportunity of studying this condition is greater than our own, may also put our hypothesis to the test. According to our belief, the importance of estimating different forms of urinary nitrogen in pernicious vomiting lies in the knowledge it may impart concerning the nutritive condition of the patient, and its value ceases at this point. Moreover, we believe that the determination of total nitrogen and ammonia nitrogen, together with the estimation of creatinin and creatin, is of much greater value (since the methods employed are accurate) in following the nutritive condition of the patient than the more elaborate plan suggested by Ewing and Wolf, in which errors are much more likely to creep in and in which undetermined nitrogen may play a misleading rôle. Slight errors in urea estimation, for instance, may give rise to high undetermined nitrogen, since an error in urea determination must be multiplied many times. In the cases to be reported only those of the chronic type are considered. All urines were preserved with toluene.

CASE I.—Mrs A., multipara, about six weeks pregnant, first seen February 15, had suffered from persistent nausea and vomiting since February 8. In this interval all food swallowed was promptly regurgitated. This attack was the third of a similar nature, the two previous seizures terminating only on emptying the uterus. Attempts to feed were unsuccessful and patient was removed to the hospital February 22. The urinary analyses are given in Table 6 and the further treatment of case in the appended clinical report.

*Discussion of Urinary Findings*.—Reference to the urinary analyses made on February 23 reveal no perversion of any of the constituents determined, and yet vomiting and nausea had been present to the extent that practically complete starvation obtained. Had no further urinary analyses been made, one would have been justified in assuming that this particular case belonged to the neurotic or reflex type of Williams, and hence was not of a serious character. These particular findings emphasize the necessity, for correct diagnosis, of analyzing the urines of consecutive days and not depending on the results obtained at long intervals of time. May it not also be possible that in some of the cases reported by Williams

the failure of the urine to show high ammonia content was due to the fact that manition had not been of sufficiently long duration or was incomplete?

Acidosis—High Ammonia The urinary analysis in Table 6 up to February 23 also shows that the mere abstinence from food for many days does not necessarily provoke a significant acidosis (high ammonia), even though the body may be in a fair state of nutrition and adipose tissue present. In our opinion the presence of fat *per se* does not necessarily play a directing rôle in the determination of urinary changes. It is to the presence or absence of carbohydrate store in the organism that we must look for the factor determining nitrogenous changes. In the starving organism but little change may be detected in the nitrogenous urinary constituents so long as the carbohydrate store is not depleted, and, in our opinion, this does not happen so rapidly as has been assumed. The sudden large increase in ammonia nitrogen on February 23 is to be explained as the result of the practically complete disappearance of glycogen. The high ammonia content is to be explained in part as originating from the perverted fat metabolism, and in part from combination with such compounds as lactic acid the latter arising from protein decomposition. On the other hand, it may be possible that the liver is unable to form urea from ammonium salts in the absence of carbohydrate,<sup>25</sup> and that these salts are excreted in the urine with substances, organic acids, which are relatively non-toxic, and which the organism readily furnishes on demand. Whichever condition obtains, it is obvious that the presence of carbohydrate is the pivot on which the whole reaction turns. Not only is lactic acid present in the urine, but acetone, diacetic acid and oxybutyric acids were demonstrated, the latter, however, falling short of the quantity necessary to account for all the ammonia, an observation which has also been noted for manition. If carbohydrate is the determining factor in the production of high ammonia content of the urine, the organism when supplied with this material should so readjust its metabolic processes that normal, or approximately normal, conditions should prevail for a time at least. If, however, the ammonia content of the urine is an evidence that the liver is out of function as a result of irremedial lesions, supplying carbohydrate to the body should not affect the ammonia output in the urine.

Influence of Carbohydrate on Urinary Picture In our cases, carbohydrate was administered as rectal enemata by the Murphy drop method. Our purpose in supplying carbohydrate was twofold first, to test the hypothesis just given, and, second, to supply easily assimilated nutri-

25 Fader Ztschr f Biol, 1877, VIII, 256

2/17	250	1014	522	041	015	0	78	29	0	No food
2/19	335		764	054	020	0	70	26	0	No food
2/20	390	1016	812	054	015	006	66	18	07	No food
2/22	630	1020	773	049	013	010	63	16	13	Admitted to hospital, persistent vomiting, no food, saline enema by drop method
2/23	610	1022	564	130	011	001	230	19	02	No food, saline drop twice, 750 cc each, persistent vomiting
2/24	670	1021	174	126	012	003	266	25	06	No food, vomits dark fluid, saline drop, dextrose drop, 500 cc 15 per cent sol
2/26	730	1021	482	187	016	0	387	33	0	No food by mouth, vomits, saline drop, dextrose drop 1500 cc 15 per cent sol, most retained
2/27	900	1017	600	246	023	0	410	38	0	No food by mouth, vomits, dextrose drop as before, most retained
3/1	830	1018	542	202	019	003	372	35	05	No food by mouth, vomits, dextrose drop 2000 cc, 15 per cent sol in 4 periods
3/2	175	1025	327	140	012	002	427	37	06	No food by mouth, drop enema, 2000 cc containing 250 cc, 30 per cent dextrose, and 250 cc whey, given in 4 periods, most retained
3/3	300	1020	216	072	010	004	333	45	18	No food by mouth, dextrose and whey drop enema as before, frequent vomiting
3/4	150	1015	324	067	016	004	206	49	12	No food by mouth, drop enema as on March 2, vomiting unchanged
3/5	380	1020	288	102	016	005	354	55	17	No food by mouth, rectal feeding continued
3/6	510	1011	321	138	016	007	425	49	21	No food by mouth, rectal feeding continued
3/7	160	1012	260	116	013	006	446	50	19	No food by mouth, rectal feeding continued
3/8	726	1014	331	157	012	011	474	36	36	No food by mouth, rectal feeding continued
3/9	850	1014	372	145	012	007	390	32	18	No food by mouth, rectal feeding continued
3/10	790	1011	358	204	009	013	570	25	36	No food by mouth, rectal feeding continued
3/11	525	1010	271	151	009	002	557	33	07	No food by mouth, rectal feeding continued
3/12	190	1010	235	133	014	009	565	59	38	No food by mouth, rectal feeding continued
3/14	110	1008	276	115	020	006	416	72	21	Uterus emptied on March 13, patient received albumin water, milk and whey, no vomiting
3/15	775	1025	305	112	014	006	367	45	19	Food Albumin water, whey, hot milk
3/16	1010	1008	333	105	016	006	315	48	18	Food Two eggs on toast, milk, tea and
3/17	1080	1010	382	106	017	007	277	44	18	Food toast
3/18	616	1010	310	066	017	002	212	54	06	Food milk

ment, because we have become convinced that the rectal administration of albumin water is of little value for the reason that in all probability very little is absorbed, and, far more important, it is not protein that the body needs. Energy is needed and from a source that requires but little effort for its assimilation, and dextrose answers this requirement fully. Not only does the organism require material which is readily transformed into energy, but inorganic salts are also a vital necessity for the proper accomplishment of the bodily functions, and this requisite cannot be met by the administration of the usual saline enemas. The fluid which is perhaps best calculated to furnish the right proportions and kinds of inorganic elements is milk, and accordingly whey has been introduced in the dextrose drip. A certain small quantity of soluble protein was thus also given an opportunity for absorption. Although from February 24 to February 28 dextrose was administered, no impression was apparently made on the urinary ammonia output. On February 28 dextrose was unfortunately omitted and the urine was not preserved and fermented. Beginning March 1 extreme care was taken with the rectal feeding and 300 grams of dextrose were administered. Assuming that all was absorbed, which is not probable, the calorific value yielded by this amount of sugar should have made some impression on the ammonia output provided our hypothesis was correct, and, indeed, there is to be observed on this day a significant fall in the total quantity eliminated, which is also true relatively. It is also of interest to note the tendency toward a lessened excretion of total nitrogen, which was, however, much more pronounced on the next day, March 2. On this day also the total ammonia nitrogen underwent a large decrease, although relatively it was greater than on March 1, which simply illustrates the fallacy of depending for diagnosis merely on percentage values. The continued administration of the rectal enemas on March 3 and 4 resulted in a still further diminution of the total ammonia nitrogen elimination, after which date the ammonia nitrogen output remained high in spite of the rectal feeding. The reduction of the absolute ammonia nitrogen from 2.46 grams to 0.67 gram (relatively 41 to 20 per cent), in our opinion, is indicative of the tenability of our hypothesis, namely, that the lack of carbohydrate is responsible for the high ammonia content of the urine in pernicious vomiting. (This will also probably explain the high ammonia in diabetes.) If lesions in the liver were the cause, it is difficult to understand how mere administration of carbohydrate could enable the hepatic cells to functionate normally. It may be objected that the salts supplied by the whey introduced replaced the ammonia which was previously combined with the organic acids. The answer to this may be obtained in part by noting that pre-

vious to the introduction of whey the ammonia nitrogen output had already begun to decrease, and in part by the fact that the quantity of organic acids in the urine during this short period had become insignificant. In other words, the ammonia nitrogen output behaved in exactly the manner that one would expect if the case were simple inanition. The inability of the organism to maintain a low total ammonia nitrogen output is explicable if one assumes that the rectal food was no longer absorbed in the same degree, or that as inanition progressed the energy need was correspondingly greater and could not be supplied by the quantities introduced, in other words, that no glycogen could be formed. The patient finally became so weak and emaciated that abortion was performed on March 13, shortly after which food was eaten in sufficient quantity to exert an appreciable influence on the ammonia nitrogen. Recovery was uneventful and the urine soon assumed its normal quantity of ammonia nitrogen. Concerning the creatinin and creatin output, little can be said. The variations in the absolute total creatinin elimination were quite large and relatively there was an increase as the total nitrogen elimination decreased, which also obtains normally. Creatin appeared in the urine at times in significant quantities, which may also probably be regarded as an evidence of inanition.<sup>26</sup>

**Acetone Bodies.** The acetone bodies, acetone, diacetic acid and oxybutyric acid were constant constituents of the urine from February 23, but the quantity of these substances present did not appear to bear a definite relation to the ammonia eliminated. Oxybutyric acid was identified by its distillation as crotonic acid, the melting-point of which was determined. Our results differ from those of Williams, who reports that "acetone, diacetic acid and oxybutyric, and allied substances were not present in the urine."<sup>27</sup>

**CASE 2**—Mrs T., primipara, about two and one-half months pregnant when admitted to hospital, had been nauseated for about one month, during the last two weeks of which nearly everything eaten had been vomited. For the week previous to entrance to hospital nothing had been retained.

**Discussion**—The details of the urinary analyses are given in Table 7. It will be observed that for the first three days on which the urine was examined the total nitrogen was high when it is considered that no food was retained, and this was taken as an indication that the body tissue was being catabolized to furnish the requisite energy. Persistent

<sup>26</sup> Benedict, Influence of Inanition on Metabolism, 1907, Carnegie Institute, Washington.

<sup>27</sup> Williams, Johns Hopkins Hosp. Bull., 1906, xxvii, 79.

TABLE 7—URINARY ANALYSES IN PERNICIOUS VOMITING OF PREGNANCY (CASE 2)\*

Date 1909	Volume c.c.	Specific Gravity	Total N Gm	NH <sub>3</sub> N Gm	Creatin N Gm	Cre- atinin N Gm	NH <sub>3</sub> N % Crea- tinin N %	Percentage of Total N as NH <sub>3</sub> N %	Percentage of Total N as Creatinin N %	Remarks
4/ 8	700	1013	7.22	1.53	0.18	0.11	21.1 %	2.5	1.5	No food for more than two weeks, headaches, Jaundice lost 20 pounds On this date cream of wheat
4/ 9	870	1010	7.36	1.83	0.15	0.10	21.8 %	2.0	1.3	
4/10	990	1012	7.00	1.98	0.16	0.11	28.2 %	2.3	1.5	Cream of wheat, crackers, clam broth, milk, toast, could take nothing sweet, vomits Food eaten as on 10th
4/11	565	1011	3.93	1.00	0.13	0.05	25.4 %	3.3	1.2	
4/12	780	1007	3.79	0.87	0.12	0.01	23.0 %	3.1	0.2	Food gradually increased, little vomiting
4/13	610	1010	3.70	0.67	0.12	0.05	18.0 %	3.2	1.1	Food gradually increased, little vomiting
4/14	700	1012	5.21	0.64	0.14	0.07	12.2 %	2.6	1.3	Food gradually increased, little vomiting
4/15	950	1017	5.13	0.46	0.17	0.04	8.9 %	3.3	0.7	Food gradually increased, little vomiting
4/16	740	1015	4.66	0.36	0.14	0.08	7.7 %	3.0	1.7	Food gradually increased, little vomiting
4/17	910	1010	4.75	0.45	0.18	0.03	9.4 %	3.7	0.6	Food gradually increased, little vomiting
4/21	1320	1006	3.17	0.40	0.15	0	12.5 %	4.7	0	Full diet, no vomiting, jaundice dis- appearing

\* Acid reaction to litmus throughout

endeavors to retain food were finally successful on April 10, although care was necessary in its administration.

Influence of Food on Urine Picture The effect of taking even the limited amount of nourishment on April 10 is at once seen in the output of total nitrogen for April 11. Such a decrease in the elimination of total nitrogen may be fairly regarded as an evidence of decreased catabolism undoubtedly resulting from the administration of a certain supply of energy from outside sources. This low nitrogen output was fairly well maintained so long as the patient was under observation. The ammonia nitrogen elimination for the first few days was high, both relatively and absolutely, and even though the absolute value fell in correspondence with the total nitrogen the relative value for the first day or two following significant food intake remained high, but quickly showed a tendency to regain the normal. Creatin was present in the urine throughout until a full diet was taken, but there was a tendency for the quantity present to diminish as soon as a noticeable food intake was inaugurated. According to our view, then, the perverted urinary nitrogen values to be observed in this case are but evidences of an insufficiency of energy-producing substances and cannot be regarded as indicative of any hepatic lesions, even though jaundice was present. If the liver were so badly damaged, why did it so rapidly acquire the property of performing its functions normally when food was given? From the fact that the patient was finally able to retain food it might be assumed that this case should be included under the reflex or neurotic type of Williams. If the vomiting observed was either of these orders, why should the ammonia nitrogen be high? For Williams says "in reflex and neurotic vomiting there are no manifest changes in the urine"<sup>28</sup>. We believe, however, that any type of vomiting of pregnancy will show the same perverted urinary nitrogen values provided food is rejected sufficiently long.

CASE 3.—*Feigned Pernicious Vomiting*.—To demonstrate this point a case may be cited in which little evidence could be gained that pernicious vomiting was present. Patient 3, primipara, was about three months pregnant, and unmarried. On admission to hospital she was markedly emaciated and all food was refused. Vomiting occurred but rarely, and then only when the patient was alone, once she was detected with her fingers inserted in her throat in an endeavor to vomit. Apparently her object was to feign pernicious vomiting of pregnancy in the hope that abortion would be performed, and thus disgrace avoided. Her recovery was rapid as soon as she received a promise of marriage from the one responsible for her condition and eventually she was delivered of a healthy child.

Without doubt her emaciation was simply a result of voluntary starvation in order to escape pregnancy and yet the urine with a nitrogen

output of 6.45 grams contained 2.15 grams of ammonia nitrogen, or 33 per cent, on April 4, 1908, and again on April 6 the total nitrogen was 4.46 grams and the ammonia content 1 gram, or 22.4 per cent. In the interim of these two analyses food was persistently urged on the patient, resulting in a diminished nitrogen output and a greater decrease in ammonia nitrogen. Somewhat later urinary analysis showed a perfectly normal output of ammonia and total nitrogen. In the hospital records this case was called "neurotic." If Williams' classification is correct, why was the ammonia nitrogen so abnormally high? According to our view, the urinary picture was merely an evidence of starvation.

CASE 4.—The patient, a primipara was in the third month of pregnancy when admitted to hospital. For two weeks previous there had been nausea followed by vomiting. There was constant distress in the region of the stomach. The patient was well nourished. The urinary analysis is shown in Table 8.

*Discussion*.—The picture presented here is strikingly similar to that of Case 2. As in that example for the first few days subsequent to admission to the hospital when the food intake was practically *nil*, the total nitrogen was high, indicating, according to our theory, an endeavor on the part of the organism to furnish energy from its protein store. The correctness of this hypothesis would appear to be indicated by the sharp and sudden fall in nitrogen output immediately following a fair ingestion of food rich in carbohydrate, and this low level was maintained fairly well so long as the urinary analysis was made. It will be observed that no attempt was made to give the patient any significant quantity of protein, since it is our belief that in conditions of weakened vitality of this sort the supply of nitrogen is a secondary consideration, for the body is well able to furnish the small amount of this element actually needed for nutritional rhythm and it is probably accomplished readily. Consideration of the ammonia nitrogen elimination shows a gradual steady decrease, which was initiated with the intake of carbohydrate-rich food. This decrease in ammonia nitrogen output can hardly be explained in any other way, since the vomiting persisted for several days after food was first given. Even on the assumption that the hepatic lesions were sufficient to call forth such an abnormally high absolute output of ammonia nitrogen, it is hard to conceive how it would be possible for the damaged cells to functionate so readily even though cessation of vomiting was established. If this hypothesis were probable, it is at least a striking coincidence that the re-establishment of normal hepatic functions should be simultaneous with the ingestion of the food. The best proof against this view, however, is to be found in Case 1 in which the ammonia nitrogen was greatly decreased without any influence on the vomiting. More-

TABLE 8—URINARY ANALYSES IN PERNICIOUS VOMITING OF PREGNANCY (CASE 4)\*

Date 1909	Volume cc	Specific Gravity	Total N Gm	NH <sub>3</sub> N Gm	Creatin N Gm	NH <sub>3</sub> N %	Percentage of Total N as Creatinin N %	Remarks	
								Creatinin N Gm	Cre- atin N %
3/18	560	1021	749	1.33		17.7	17.7		No food for two weeks, vomited, only albumin water given this day, vomited
3/21	595	1021	753	1.66	0.13	0.15	22.0	1.7	Only albumin water given this day, vomited
3/22	690	1022	874	2.09	0.21	0.11	23.9	2.4	Clam broth and albumin water retained, vomited
3/23	610	1017	783	1.95	0.12	0.15	24.9	1.5	Gruel and milk sugar 3 times, clam broth, albumin and milk sugar, oyster stew, vomiting continues but food retained
3/24	310	1013	439	0.98	0.11	0.04	22.3	2.5	Cream of wheat and milk sugar, ice-cream, clam broth, albumin water, cream, vomited
3/25	385	1016	504	0.95	0.10	0.09	18.8	1.9	Food as before, milk sugar omitted, headaches, vomited
3/26	475	1015	556	1.18	0.12	0.10	21.2	2.1	Cream of wheat, milk, cracker, oyster stew, wine jelly, no vomiting
3/27	390	1018	468	1.00	0.14	0.05	21.4	2.9	Cream of wheat, milk, toast, ice cream, cream, vomited once
3/28	100	1018	439	0.76	0.13	0.04	17.3	2.9	Cream of wheat, baked potato, cream, cream toast, oyster stew, vomited twice
3/29	120	1015	386	0.62	0.13	0.04	16.1	3.3	Cream of wheat, baked potato, cream, cream toast, no vomiting
3/30	555	1019	316	0.42	0.14	0.02	13.2	4.4	Cream of wheat, baked potato, cream, cream toast, vomited once
3/31	650	1012	447	0.39	0.18	0	8.7	4.0	Diet as on 28th, plus small amount sweet-bread, no vomiting
4/1	520	1018	409	0.39	0.18	0.03	9.5	4.4	From this point more solid food was given, no vomiting
4/2	695	1013	279	0.28	0.12	0	10.0	4.2	No vomiting
4/3	1225	1011	617	0.57	0.21	0	9.2	3.4	No vomiting
4/8	720	1018	402	0.32	0.12	0	7.9	2.9	No vomiting, patient out of bed April 24, discharged April 30 and apparently normal

\* Acid reaction to litmus up to and including April 1, alkaline April 2-8

over, the liver cells must have been almost completely disorganized to have been unable to perform their function of forming urea, for Jackson and Pearce<sup>29</sup> and Underhill and Klemer<sup>30</sup> have shown the great difficulty of attaining this object by the production of experimental hepatic lesions. It is only when practically all the liver cells are destroyed that any abnormality in urea formation is to be observed. The presence of a few cells is apparently sufficient to carry on this function, and the recorded observations have tended to emphasize this as one of the many factors of safety to be found in the body. On the other hand, abstinence from food readily induces a perversion in urea formation, particularly when the carbohydrate store of the body is low. It is probable, therefore, that the perversion in urea formation found in inanition should also be regarded as a factor of safety, the function of which is to maintain an equilibrium between the acids and bases of the body. With one or two exceptions, the absolute quantity of creatinin nitrogen excreted in Case 4 was remarkably constant, but the relative values were quite variable. Creatin nitrogen, on the other hand, showed little regularity of elimination. As soon as food was introduced into the body a tendency toward a diminution in creatin excretion was observed. Since the food consisted in large measure of carbohydrate, it is obvious that this foodstuff is capable of causing such an action. Indeed in some unpublished experiments by one of us (Underhill) and W. C. Rose, it has been shown that creatin in the urine of fasting rabbits can be made to disappear rapidly by administration of sugar.

From the behavior of the urine in the few examples of vomiting of pregnancy here submitted, we feel justified in offering the hypothesis previously outlined, namely, that the perverted nitrogen ratios which occur can be regarded only as evidences of lack of energy-producing materials, carbohydrates, and that so long as sufficient carbohydrate is administered no such perversion will occur. The determination of these ratios is, therefore, of value, not as a means of diagnosing the progress or severity of the pathological condition, but as an index of the nutritive condition of the body.

*Relation of Inanition to Structural Changes in the Liver.*—While it is entirely without our province to attempt to explain the etiology of pernicious vomiting, yet since so much emphasis has been laid on the rôle played by the liver in this connection it is not out of place to inquire what influence starvation exerts on the cellular structure of this organ. Does starvation produce pathological changes? In an investigation with

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29 Jackson and Pearce *Jour Exper Med.*, 1907, **iv**, 552  
 30 Underhill and Klemer *Jour Biol Chem.* 1908, **iv**, 165

Mr. W C Rose, rabbits were allowed to die from inanition. The livers of some of these animals showed "a marked focal necrosis, reminding one almost of what is seen in intoxication with hemagglutinins"<sup>31</sup> So far as we are aware, there is practically no literature on this point, and, in view of the above results on normal animals, it may be inferred, perhaps, that a part of the pathological changes observed in the liver in pernicious vomiting can be explained as a result of disordered nutrition due to starvation, which must play a prominent rôle in the prolonged cases. From both the chemical and anatomical viewpoints, therefore, starvation is a factor in pernicious vomiting to which more attention should be paid before ascribing to other less well-known processes positions of greater prominence.

#### CONCLUSIONS

Contrary to the opinions expressed by Stone, Edgar, and Ewing and Wolf, a critical review of the literature relative to the composition of the urine in pernicious vomiting of pregnancy fails to reveal adequate evidence of either suboxidation or deficient desamidation. A different interpretation has been made of the results obtained by the above investigators.

The composition of the urine in pernicious vomiting is strikingly similar to that which obtains in the urine eliminated during inanition. In both instances the characteristic perversions are changed relations in the excretion of urea and ammonia and at times in the output of creatinin and creatin. Other changes previously reported in the nitrogen output have not been firmly established. The determination of nitrogen, ammonia, creatinin and creatin in pernicious vomiting is believed to be of greater value than the more elaborate plan suggested by others, inasmuch as the methods to be employed are accurate.

It is suggested that the changes observed in the urine in pernicious vomiting of pregnancy are induced by the accompanying inanition. Evidence tending to substantiate this view is furnished by the observation that the perverted urinary nitrogen relations rapidly resume the normal on administration of food without necessarily exerting any influence on the pathological state of the patient.

In pernicious vomiting of pregnancy where inanition is a significant factor, the administration of energy-yielding foodstuffs is of greater value than the giving of foods rich in nitrogen. The body is capable of furnishing the small quantity of nitrogen requisite for nutritional

<sup>31</sup> Report from Dr H Gideon Wells of the University of Chicago to whom we are under obligations for the histological examination of the tissues of these animals.

rhythm, but, in the absence of carbohydrate, energy-yielding substances present in the body are difficult of utilization. It is, therefore, suggested that the employment of enemas of dextrose solutions by the Murphy drop method is a more rational proceeding in this and related conditions than attempts to administer the usual albumin solution, which in all probability is not absorbed and for which the body has relatively little need.

Carbohydrate supply is apparently the factor determining the relative output of urea and ammonia, since in pernicious vomiting of pregnancy, as in inanition, the administration of this substance by mouth or by rectal enemas is followed by a distinct tendency toward a resumption of the normal elimination of these compounds.

#### CLINICAL REPORT (IN ABSTRACT) OF FOUR CASES OF VOMITING OF PREGNANCY

**CASE 1**—Patient is a Jewess, aged 25, blonde, fourth pregnancy. Complaint Nausea and vomiting.

**History**—The patient was always well except for two previous attacks of severe nausea and vomiting of pregnancy, necessitating abortion. Onset of the menses occurred at 13 years, regular and normal. The patient was married in 1903, had one child, born one year later. She had severe nausea and vomiting in the early months of this pregnancy, but not nearly so severe as in the subsequent pregnancies. She was delivered at term of a healthy child, now living and well. In the winter of 1905-06 she was pregnant for the second time and had such severe nausea and vomiting that she was sent to the New Haven Hospital, where the uterus was emptied. The case was classed clinically as pernicious vomiting of pregnancy. On August 5, 1907, she was again admitted to the hospital on account of vomiting in her third pregnancy. At this time she was about six weeks pregnant and had been vomiting for three weeks. She vomited all food and liquids, including water, taken by mouth, and vomited also, independent of the taking of food. On admission the ammonia nitrogen was 2.73 gm., or 40.7 per cent of total nitrogen. This decreased steadily while under observation until August 12, when the figures were 1.85 gm. (26 per cent). Normal saline, egg albumin, and pasteurized milk were given per rectum. During this period, however, the general condition of the patient steadily grew worse, her pulse became more rapid and weak, lips and tongue dry, cracked and coated, breath fetid, mental condition bad, and the skin took on a yellowish tinge. The uterus was emptied August 13, four weeks after onset of vomiting. The patient improved rapidly after the operation and insisted on leaving the hospital on the tenth day, when she was in fair general condition.

**Present Illness**—Last menses Dec 31, 1908. Onset of nausea and vomiting February 8, 1909. The patient was first seen February 15, has eaten practically nothing for the past week as everything swallowed distresses her and is vomited. She vomits two or three times daily independent of the taking of food.

**Examination**—Well-nourished, well-developed young woman, skin and mucous membranes fair color, tongue clean and moist. Temperature 97.4. Pulse 80, regular, fair volume and tension. Chest and abdomen negative. Good perineum, cervix soft, large, slight bilateral laceration, body of uterus enlarged and retroverted. Retroversion readily corrected.

*Treatment and Course of Disease*.—For two days there was a slight decrease in the nausea and vomiting, only to be followed by a period of severe vomiting and retching. Attempts at feeding were unsuccessful. Patient sent to hospital February 22. Saline drop enema (per rectum) was given for two days, then from February 24 to March 1 the patient was given 1,500 cc of a 15 per cent dextrose solution every twenty-four hours, by the drop method, in addition to about 300 cc of saline. From March 2 to March 13, 1,000 cc of 30 per cent dextrose and 1,000 cc of whey were given each day. During the first week in the hospital the urine increased markedly in amount, there was a slight improvement in the patient's general condition, she was more cheerful and hopeful of completing her pregnancy. The vomiting continued but was not severe. Nothing but a little water was given by mouth and this was occasionally retained. By March 3 the urine again became markedly diminished in amount in spite of the fact that the patient received and retained an abundance of fluid per rectum. From March 4 a gradual failure in her condition could be noted from day to day. She became apathetic, her pulse increased in rate and became of poor quality. The skin took on a yellowish tinge. On March 8 her lips were dry and cracked and the gums were beginning to bleed a little. By March 13 her lips and teeth were covered with bloody sores and her condition had become so serious that the uterus was emptied, five weeks after onset of vomiting. Her temperature was normal throughout this period and her pulse curve showed a gradual rise from 80 on entrance to 110 on the 11th, 12th, and 13th. Respiration 20 throughout. The vomiting ceased immediately after the operation and there was a noticeable improvement in her condition in twenty-four hours. She took nourishment by mouth on the following day, ate a poached egg on toast on the third day, and made a rapid convalescence, leaving the hospital April 1 in good condition.

**CASE 2.—Patient was a blonde, aged 25. Complaint vomiting.**

*History*.—The patient was born in the United States of French parents. She had measles and mumps as a child, no other illness, was always well and strong, habitually constipated, does not use alcohol. Menses began at 13 years, always regular and normal. The patient had been married one year, this was her first pregnancy. Last menstruation January 20, 1909.

*Present Illness*.—About February 20 the patient began to have morning nausea and frontal headaches, vomited rarely. This continued for about three weeks and then ceased entirely. On March 22, nausea and vomiting began again with increased severity. In the course of a week she was unable to keep anything on her stomach. She was admitted to the hospital April 5, 1909. No food has been retained for over a week, lost twenty pounds in weight in last two months. Urine decreased in amount.

*Examination*.—On entrance. Young woman, well developed, fairly well nourished, skin rather flabby and with a slight yellow tinge, sclerae distinctly yellow, tongue clean and moist. Abdomen soft, not distended, slightly tender in hypogastric region and over Bloodgood's point. Liver dulness extends from fourth rib to a point 4 cm above costal margin in nipple line. Gall-bladder not palpable. No tenderness along right costal margin, or in epigastrium. Fundus of uterus 3.5 cm above symphysis. No edema of feet or legs. Reflexes normal.

*Treatment and Course of Disease*.—Patient vomited six to three times a day for the first ten days in the hospital, then once a day for a few days and after that not at all. Pulse was rapid (140 to 116) and weak for seven or eight days, then fell to 100 and to 80. Temperature and respirations normal throughout. She was very nervous and restless at first and morphin was necessary for twelve days to induce sleep. Stools normal color at all times. Albumin water was given

by mouth at first in small quantities at frequent intervals and retained. Food was gradually increased. Gruels, broths, etc., were soon taken and at the end of the second week she ate a chop. Saline enemas were given from the start. The patient had a marked antipathy for sweet things and it was impossible to feed her sugar, dextrose or lactose. Even plain water tasted sweet and nauseated her. Carbonated waters, cream of tartar waters, and orange juice were well taken. Styrchnin and chloretone were given from the start. Her bowels were moved at first by calomel, after that sodium phosphate in dram doses t i d acted well as a laxative. The jaundice disappeared by the end of the second week and the patient made a good recovery, leaving the hospital May 8 in good condition. She took a general ward diet during the last two weeks of her stay.

**CASE 3**—Patient is of American parentage, aged 34, blonde, primipara, unmarried. Complaint vomiting.

*History*—The patient had diseases of childhood, frequent attacks of chills and fever from girlhood. Diphtheria one year ago, grippe two months ago. She generally has fair health, but usually constipated. Onset of menses occurred at 14 years, regular, normal.

*Present Illness*—Last menses occurred December 16. Onset of nausea and vomiting about February 22. Vomiting occurs right after eating and also independent of the taking of food. Though she has been vomiting but two or three times daily she has taken so little food that she has become very thin and weak. Vomiting is frequently followed by severe retching.

*Examination*—On admission to the hospital March 22, patient was markedly emaciated, voice weak and high-pitched. Temperature 99, pulse 98, poor quality, respirations 24. Skin and mucous membranes pale, tongue coated, breath fetid. Urine decreased in amount, trace of albumin, high percentage of ammonia nitrogen (33 per cent), no casts. She is constipated. Uterus enlarged to about size of three months pregnancy.

*Treatment and Course of Disease*—In spite of the seriousness of the patient's condition and of the urinary findings, it was felt that this was not a case of pernicious vomiting. It should be noted that the pregnancy was very unwelcome and the patient was anxious to have an abortion induced. Further, she believed that this would be done if her condition became serious. There was a strong suspicion that she had deliberately starved herself in order to attain her wish in the matter. Under a strict régime there was a slow but progressive improvement in the patient's condition. Vomiting occurred but once a day during the first week of her stay in the hospital and then only when she was alone. Finally she was caught with her finger in her throat. Vomiting ceased entirely shortly after this. In six weeks she was taking a satisfactory amount of nourishment and had gained sufficiently in strength to get up and out of doors. The patient left the hospital in fair condition in May. The further course of her pregnancy was uneventful and she was delivered at term of a healthy child. Small amounts of albumin in water and milk were given at first, there was gradual increase of these with addition of jellies and gruels, etc., until she partook of a general diet. Medicines given were chloretone, gr 1, t i d, laxatives as needed.

**CASE 4**—The patient is a blonde, aged 30, of American parentage.

*History*—The patient had diseases of childhood only, was usually constipated. The menses began at 13 years, regular, some dysmenorrhea. The patient has been married three years, this is her first pregnancy, last menstruation January 19. She was admitted to the hospital March 17.

*Present Illness*—Onset of severe nausea occurred about two weeks ago, accompanied in a few days by vomiting after eating. Since onset patient has had a constant feeling of distress in epigastrium, nearly constant nausea, and for ten days she has vomited after nearly every attempt to take food. Appetite is very poor, bowels irregular and constipated. For two days before admission she vomited all food and several times vomited between attempts at eating.

*Examination*—On admission Well-developed, well-nourished young woman. The skin and mucous membrane of good color. Tongue with grayish coating down center, margins clear. Heart and lungs negative. Abdomen soft, not distended, somewhat tender in epigastrium. Liver dulness from fourth rib to costal margin. Slight edema above ankles. Patella reflexes exaggerated. Temperature 97.6. Pulse 80, regular. Fair volume, easily compressed. Respirations 20.

*Treatment and Course of Disease*—The patient was distressed by nausea and vomiting for the first week of her stay in the hospital, but managed to retain an increasing amount of nourishment. After this the vomiting practically ceased, though the nausea continued for two weeks longer. The patient was given albumin water, clam broth, a mineral water and ginger ale in small amounts for six days. On March 23, she took 2 ounces of gruel with  $\frac{1}{4}$  ounce of milk sugar, 3 ounces of oyster stew, and 6 ounces of albumin water. Increasing amounts of carbohydrates were gradually added to this diet. After April 4 the diet was a pretty general one, though limited in amount. The patient's appetite was fair and food was relished. She made a slow but uneventful recovery and left the hospital April 29 in good condition.

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# THE EFFECT OF DIGITALIS ON THE VENTRICULAR RATE IN MAN \*

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Of the various cardiac irregularities produced experimentally by digitalis, the earliest to appear in most instances is an occasional omission of ventricular contractions, owing to an interruption of the stimulus between the auricles and ventricles. Somewhat later, or even immediately after this, the heart may assume a most peculiar rhythm in which the auricles and ventricles are beating quite independently of each other<sup>1, 2</sup>. This irregularity differs from the ordinary rhythm of complete heart-block in that the ventricular rate is not slow, but approaches and, indeed, usually exceeds the auricular rate, so that, for example, one may count sixteen ventricular to fifteen auricular contractions. This rhythm is so common in carefully graded digitalis poisoning in dogs that it has become a regular portion of the pharmacologic demonstrations given by Dr Edmonds to the University of Michigan students and by Professor Hatcher to the Cornell University students. So far as we know, this form of irregularity has never been described in man. Its probable occurrence in the patient whose history follows has led us to report the case and to discuss briefly the effect of digitalis on the ventricular rate in man.

CASE 1.—*Patient*—A teamster, 27 years old, entered the first medical division of Bellevue Hospital, New York, on June 27, 1908, complaining of cough and dyspnea. His family history was negative. He had had acute articular rheumatism at 12 years, a suspicious venereal sore at 22, and had been a heavy drinker up to five months before admission. For two years he had been troubled with shortness of breath on moderate exertion, but in the past two months this had become much more severe and was often paroxysmal in character. He had a loose cough and at times slight fever. No edema.

*Examination*—This showed a well-nourished young man suffering from dyspnea. The cardiac dulness was not enlarged, the heart-sounds were clear and of

\* Read at a meeting of the Section on Medicine of the New York Academy of Medicine, Oct 19, 1909

1 Cushny, A R. The Action of Substances of the Digitalis Series on the Circulation in Mammals. Jour Exper Med., 1897, 11, 233

2 Tabora. Ueber die experimentelle Erzeugung von Kammersystolenausfall und Dissociation durch Digitalis. Ztschr f exper Path u Therap., 1906, 111, 549

normal intensity. The lungs showed a diffuse bronchitis, and, in addition, the left lower axilla showed dulness, diminished breath sounds, diminished fremitus, and numerous crackling rales. The liver was palpable at the level of the umbilicus. The urine showed a heavy cloud of albumin with a specific gravity of 1,020 and many hyaline and granular casts. He was discharged on July 10 considerably improved.

*Course of Disease.*—On Aug. 3, 1908, he was readmitted to the second medical division of Bellevue Hospital complaining of dyspnea. His heart was now distinctly enlarged, the apex-beat being in the sixth intercostal space, 15 cm from the mid-line, with the right border 2 cm beyond the sternal margin. There was a soft systolic murmur at the apex transmitted to the axilla and back. The second pulmonic sound was accentuated. The pulse was weak, of small volume, and occasionally irregular. The urine was at times negative, at other times it showed traces of albumin. The feet were swollen. During this stay in the hospital he ran a slight but continuous fever, occasionally reaching 100.5, and toward the end 102. His blood showed a mild anemia, with 9,000 to 11,000 white blood corpuscles. Blood cultures were negative. He died on September 5. There was no autopsy. The clinical diagnosis was chronic myocardial insufficiency with dilatation.

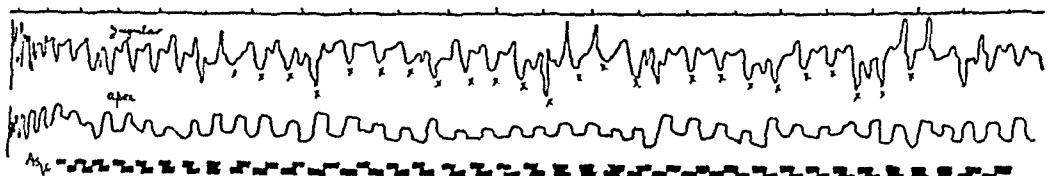


Fig. 1.—Jugular and apex tracing with chart showing the relation of auricular and ventricular systoles, 1/15 second being allowed for the venous waves to reach the neck.

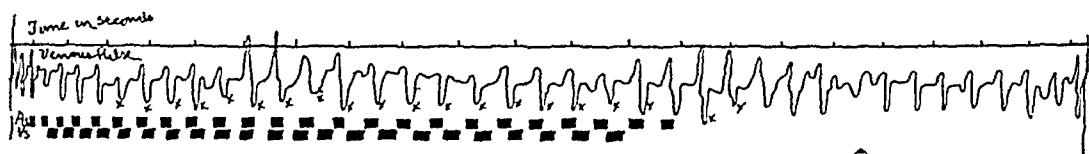


Fig. 2.—Same as Figure 1, except that the apex tracing was too indistinct for reproduction.

During the earlier part of the patient's second stay in the hospital, his venous pulse was of the usual negative type, the well-marked *a* waves indicating normal auricular contractions. On Sept. 4, 1908, one day before he died, the patient's general condition had become much more serious and his edema and dyspnea more severe. At times gallop rhythm was heard over the precordia. The venous tracings taken on this day were remarkable in that they showed a regularly recurring cycle of changes (Figs. 1 and 2). Each cycle required about seven seconds for its completion, and included about fourteen ventricular contractions. At certain portions of the cycle a single, sharp, positive wave occurred in the jugular pulse just after the onset of ventricular systole. Midway between

these groups of sharp waves, each ventricular systole was represented on the venous pulse by two waves of almost equal height connected by a more or less distinct plateau. It was evident from the duration of these cycles (seven seconds) that they were independent of the respiration, for the respiratory rate was constantly about 30 per minute.

In our opinion, the explanation of these cycles is to be sought in the interference of two systems of waves which were independent of one another and not quite synchronous. The one system is best represented on our venous tracings by the negative waves marked  $x$ , which recur regularly and nearly always distinctly. The other is represented by the apex-beats. A comparison between these two shows that the former recur at a slightly slower rate than do the latter, so that, for example, thirteen  $x$  waves correspond to fourteen apex-beats. There was evident, therefore, a lack of synchronism between the apex-beats representing the systoles of the left ventricle and the portion of the heart which caused the  $a$  waves. Several reasons can be advanced against the view that these latter were due to the contractions of the right ventricle. In the first place a dissociation of this character between the two ventricles is unknown experimentally and would be highly improbable on theoretical grounds. In the second place, such a dissociation ought to cause recurring variations in the shape of the apex-beat which were not present in our tracings. Finally, it is difficult to explain the rhythmical changes in the venous pulse on this hypothesis.

It is much more probable that the negative  $x$  waves were due to auricular diastoles and that the cyclic variations in the venous pulse were caused by a lack of synchronism between the auricles and ventricles of such a nature that for thirteen auricular there were fourteen ventricular contractions. On this assumption these cycles in the venous pulse become clear. The positive wave, which can usually be distinguished just before the  $x$  wave, was in each case due to the auricular contraction, the other waves were caused by the contractions of the right ventricle, and the changing character of the venous pulse was due to the complicated interference of the two systems of waves. Unfortunately, it is not always possible to identify the individual waves on the venous tracings. Yet one thing comes out clearly when a diagram is constructed to show the relation of auricular and ventricular contractions according to this hypothesis (Figs 1 and 2). This is the fact that the single high waves on the venous pulse occurred when the onset of ventricular systole coincided with that of auricular systole. Such single high waves are common in those extrasystoles where premature ventricular contractions coincide

with auricular systoles,<sup>3</sup> and their occurrence in our tracings just where one would theoretically expect them strengthens our hypothesis.

Through the kindness of Dr C W Edmonds, tracings were obtained from the internal jugular vein of a dog during digitalis poisoning, at the stage where the ventricular contractions were slightly more rapid than the auricular (Fig 3). This venous tracing, though not precisely similar to those obtained from our patient, resembles them in the prominence of the  $\gamma$  waves due to auricular diastole and in the occurrence of single waves when the onset of ventricular systole coincided with that of auricular systole. In these particulars, therefore, it supports our interpretation of the tracing obtained from man.

We have already stated that this peculiar rhythm is frequently observed in the later stages of experimental digitalis poisoning. On inquiry it was found that the patient from whom our tracings were

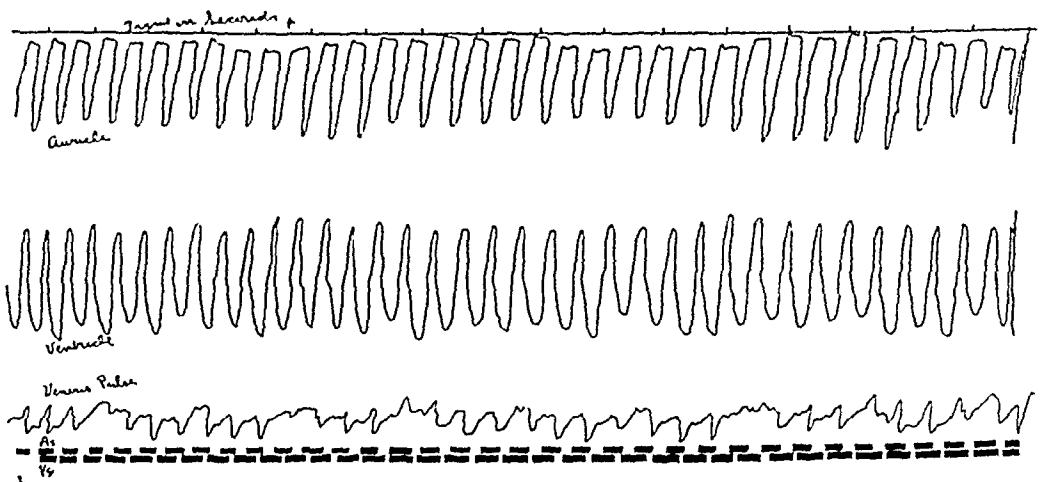


Fig 3.—Dissociation of auricles and ventricles produced experimentally by digitalis, with auricular, ventricular and venous tracings. The main negative waves of the venous pulse coincide with auricular diastole and the single positive waves with the simultaneous onset of auricular and ventricular systole.

obtained had been taking drugs of the digitalis series in considerable quantities over a long period of time. From August 8 to August 16 he took daily one dram of the tincture of strophanthus, from August 18 to August 28 one-half dram daily of the tincture of digitalis, on August 29 six minimis of the fluidextract of digitalis, on August 30 two minimis of the fluidextract of digitalis. From August 31 to September 2 he took fifteen minimis of the tincture of digitalis and thirty minimis of the fluidextract of apocynum daily, on September 3, 4 and 5 thirty minimis of the

<sup>3</sup> Hewlett, A W. The Interpretation of the Positive Venous Pulse. Jour Med Research, 1907, *vii*, 119.

fluidextract of apocynum, and in addition on September 4 and 5 eighteen minims of the fluidextract of digitalis. During all this time his heart failure was gradually becoming worse and he died on September 5. Although the daily amount of digitalis and its allies did not seem excessive, especially from August 16 up to September 4, nevertheless in view of the fact that the type of arrhythmia corresponded to that seen in experimental digitalis poisoning, it seems probable to us that the irregularity was due to a cumulative action of the drug. If this be true, it illustrates how difficult it may be to ascertain when enough digitalis has been given, for at no time was marked slowing of the pulse observed.

This peculiar irregularity is believed to be due to the action of digitalis in increasing the spontaneous ventricular rate. Ordinarily these chambers take their rhythm from the auricles and their tendency to contract spontaneously is held in abeyance. Should stimuli from the auricles fail to reach them, however, sufficient time may elapse for the ventricles to develop their inherent rhythm. In complete heart-block, for example, they contract spontaneously and regularly at a rate of about thirty per minute. Tabora<sup>2</sup> has shown that this spontaneous ventricular rhythm, induced experimentally by section of the His bundle, may be doubled by the administration of digitalis, and, furthermore, that during the pauses of a partial heart-block the ventricles may give one or more spontaneous contractions at a rate which shows that their inherent rhythm has been increased. Erlanger<sup>4</sup> has also noted the increased ventricular rate produced by digitalis during complete experimental heart-block.

We have endeavored to find in the literature similar examples of digitalis action on man. Several instances have been recorded where the ventricles contracted spontaneously during a partial heart-block and it seemed of interest to see if these spontaneous contractions showed a ventricular rate greater than the normal and also to note their relation to the administration of digitalis. Rihl's patient had a partial heart-block, which was apparently due to the administration of digitalis.<sup>5</sup> In the long pauses which occurred during the blocks the ventricles at times contracted spontaneously. These spontaneous contractions occurred 1.8 to 2 seconds after the normal ventricular contractions, thus corresponding to a spontaneous rate of thirty to thirty-three per minute. Apparently, therefore, although the digitalis produced a partial heart-block in this patient,

<sup>4</sup> Erlanger, J. Ueber den Grad der Vaguswirkung auf die Kammern des Hundeherzens. Arch f d ges Physiol, 1909, cxxvi, 77.

<sup>5</sup> Rihl. Klinischer Beitrag zur Kenntnis der Ueberleitungsstorungen von der Bildungsstätte der Ursprungsreize zum Vorhof. Deutsch Arch f klin Med, 1908, xciv, 286.

it did not increase the automatic ventricular rate. In a similar case report by Mackenzie<sup>6</sup> the ventricular pause of two seconds corresponded to a rate of thirty. No statement was made as to whether this patient was under the influence of digitalis. Joachim's<sup>7</sup> patient had taken digitalis, though the amount is not stated. His tracings admit of an interpretation similar to those just cited and this would make the ventricular pauses in his patient about 13 seconds and the ventricular rate about 46. Finally, in the case reported by Wenckebach,<sup>8</sup> spontaneous ventricular systoles occurred during partial heart-block at intervals of 13 seconds corresponding to a spontaneous rate of forty-six per minute. Wenckebach states that his patient had been taking the tincture of strophanthus, but he does not express an opinion as to any possible relation between the drug and the spontaneous ventricular contractions. In these last two cases the ventricular rate was distinctly faster than normal. So far as we may judge from the literature, therefore, spontaneous ventricular contractions are not common in man during partial heart-block caused by digitalis, and when they do occur they may or may not show an increased ventricular rate.

Of particular interest in this regard is the effect of digitalis on the ventricular rhythm in complete heart-block. Clinicians are not agreed as to its therapeutic value in this condition, some favoring its use in certain cases,<sup>9</sup> others advising caution in its administration.<sup>10</sup> Its deleterious action in producing or increasing a partial block has no bearing on its value when the block is complete. Neither is the slow heart-rate a contraindication to its use, for, so far as we know, digitalis does not slow the automatically beating ventricles either in animals or man. On the other hand, one might conceive that digitalis would be beneficial to patients with complete heart-block by increasing the force of the ventricular contractions or by increasing the automatic ventricular rate, or that the latter might serve as a therapeutic indicator of the effect of the drug. So far as we know, this possibility has not been considered by clinicians, and a definite increase of ventricular rate has not been observed during the therapeutic administration of digitalis to patients with complete heart-

<sup>6</sup> Mackenzie, J. The Cause of Heart Irregularity in Influenza. Brit Med Jour., 1902, ii, 1411.

<sup>7</sup> Joachim, G. Ein atypischer Fall von Störung der Reizleitung im Herzmuskel. Berl klin Wochenschr., 1908, xiv, 911.

<sup>8</sup> Wenckebach, K F. Beiträge zur Kenntnis der menschlichen Herzaktivität, III Teil, Arch f Anat u Physiol Physiol Abteil, 1908) (Suppl.), 53.

<sup>9</sup> Gibson, G A. Bradycardia. Edinburgh Med Jour., 1905, xliii, 9.

<sup>10</sup> Osler, W. The So called Stokes-Adams Disease. Lancet, 1903, ii, 516.

block Bachmann,<sup>11</sup> for example, found that, while strophanthus moderately slowed the auricles of his patient, it did not influence the ventricles.

In view of the meager clinical data on this point, we shall report a case of complete heart-block in which active preparations of digitalis were given in fairly large doses over a considerable period.

**CASE 2—Patient**—A laborei, 60 years old, was admitted to the second medical division of Bellevue Hospital on Nov 27, 1908, having been picked up in the street during a period of unconsciousness. He had used alcohol regularly and at times to excess, and had had no infectious diseases except gonorrhea and a venereal sore.

**Examination**—This showed an enlarged heart with an accentuated second aortic sound and a blowing systolic murmur over the apex region. The radial arteries were markedly thickened, and the pulse-rate was usually about 33 per minute.

**Course of Disease**—While in the hospital he had a number of typical convulsive attacks. Of the many venous tracings taken during his stay the great

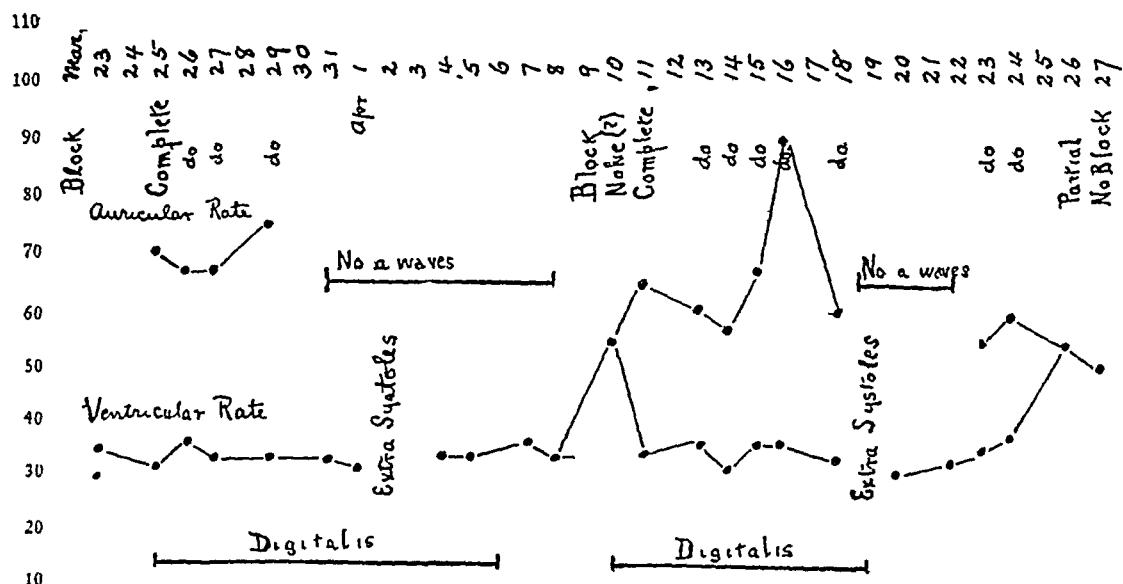


Fig. 4.—Chart showing effect of digitalis on the auricular and ventricular contractions of a patient with heart-block.

majority showed a complete heart-block, although at times there was a partial heart-block or none at all. The first course of digitalis, consisting of one-half ounce of the infusion four times a day was begun on March 18, 1908, and terminated on April 6. Venous tracings were taken almost daily and the auricular and ventricular rates as calculated from these are shown on the accompanying chart (Fig. 4). The auricular waves, which were easily recognized on the earlier jugular tracings disappeared on March 31 and did not reappear until April 10 or 11. On April 2 the apex tracings showed a ventricular arrhythmia which was due to a regular recurrence of normal and slightly premature beats.

The second course of digitalis (15 minimis of the tincture four times daily) began April 10 and was terminated on April 19. On the latter day the auricular

11 In a later case Bachmann (THE ARCHIVES INT MED., 1909, iv, 238) obtained a slight acceleration of the ventricles, under strophanthus, and a marked improvement in his patient's condition.

waves again disappeared and did not return until April 23. On the 19th also the ventricles assumed a bigeminal rhythm, similar to that observed on April 2 except that the premature beats came earlier. At times this bigeminus was continuous (Fig. 5), at other times the premature contractions occurred after every other long interval (Fig. 6).

A study of the latter tracing shows that the premature contraction occurred 0.66 second after the normal, that the next interval was about 1.66 second, while the final interval was about 1.83 second. The intervals following the extrasystoles were always slightly shorter than those separating the normal beats. It is usually stated that ventricular extrasystoles occurring during complete heart-block are followed by the same intermission as occurs between normal beats, there being no compensatory pause. However, a slightly shortened period such as we observed on our apex tracings has been noted by others on radial tracings.<sup>12, 13</sup> Their explanation, viz., that the extra systole is delayed in its transmission to the wrist, could not be applied to our patient.

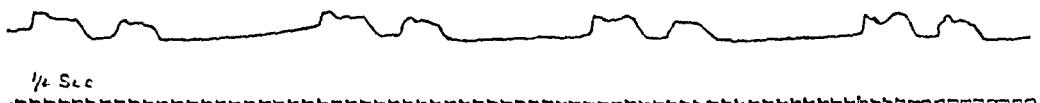


Fig. 5.—Bigeminal rhythm during digitalis administration to a patient with complete heart-block

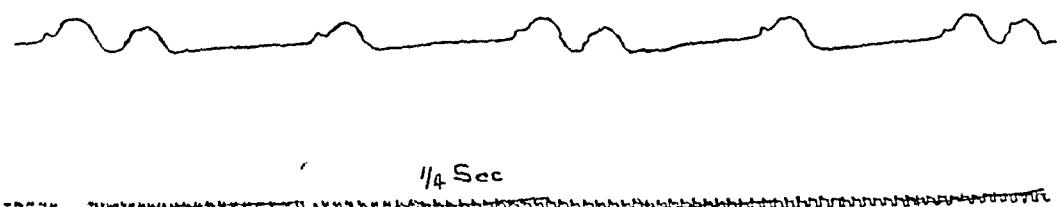


Fig. 6.—Extrasystoles after every other normal beat in same patient

Shortly after the second course of digitalis, possibly also after the first, the heart-block was diminished, for, on the 26th, there was a definite partial block and on the 27th no block at all. It is possible that the diminution of the block bore some relation to the administration of digitalis.

No increase in the regular rate of the ventricles occurred during our administration of digitalis to this patient; and yet it seems probable that his heart showed some effects from the drug. The disappearance of the a waves from the jugular was at first regarded as a defect in technic, but their second disappearance from the apex tracings during the second

<sup>12</sup> Wenckebach, K. F. Kenntnis der menschlichen Herzatigkeit Arch f Anat u Physiol, Physiol Abteil, 1906, 297

<sup>13</sup> Gossage, A. M. Complete Heart Block Quart Jour Med, 1908, 11, 19

course of the drug suggested that this may have been due to a toxic weakening of the auricular contractions. The appearance of the extra systoles on each occasion also suggested a digitalis effect. It is impossible, of course, to draw conclusions from this single experience, though it indicates that moderately large doses of an active preparation of digitalis may fail to increase the ventricular rate in patients with complete heart-block and that, therefore, one cannot rely on such an increase as a guard against an overdose of the drug in these patients.

In conclusion, we wish to thank Professors W Gilman Thompson and C L Dana, in whose services at Bellevue Hospital these patients were observed and by whose permission their histories are reported.

## EMPHYSEMATOUS GANGRENE DUE TO A MEMBER OF THE COLON GROUP

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Cases of gangrene accompanied by gas formation in the tissues have been observed for a good many years. Such cases are most common after tearing and lacerating wounds, compound fractures with extensive injury of the tissues, though they may follow slight cuts, abrasions or puncture wounds.

The condition was first accurately described in 1853 by Maisonneuve,<sup>1</sup> who called it "gaseous phlegmon."

The proof of the infectious nature of the process we owe to Bottini, who in 1875 by inoculation experiments successfully showed this characteristic. While the disease was recognized as an infectious process, it was not until the work of Pasteur in 1877 that any definite etiological factor was described. He isolated from such a case an organism called by him *vibrio septique*, but later given the name of *Bacillus edematis maligni* by Koch and Gaffky. This was the first pathogenic anaerobe discovered. This organism was thought to be the main factor in these cases. Such especially has been the view in France, but while cases showing gas formation in tissues of man due to this organism undoubtedly do occur, too much importance by far has been attributed to this germ, and in general careful bacteriological work has been neglected. Guillemot,<sup>2</sup> Muir and Ritchie,<sup>3</sup> and Brabec<sup>4</sup> have reported cases in which this organism was undoubtedly the etiological factor. By far the most important causative agent in emphysematous gangrene and allied conditions is the organism isolated and described by Welch and Nuttall<sup>5</sup> in 1891 and named by them *Bacillus aerogenes capsulatus*, or better termed *Bacterium welchii* (Migula). This organism was independently described by E Fraenkel<sup>6</sup> in 1893 and called by him *Bacillus phlegmone emphysematosæ*, but later he acknowledged it to be identical with *Bacterium welchii*. The same

1 Maisonneuve Gazette méd de Paris, 1853, p 592

2 Guillemot, L Compt rend Soc de biol, Paris, 1898, x, 1017

3 Muir and Ritchie Manual of Bacteriology, American ed, N Y, 1904, MacMillan Co

4 Brabec Wien klin Rundschau, 1900, xiv, 145 and 167

5 Welch, William, and Nuttall Bull Johns Hopkins Hosp, 1892, iii, 31

6 Fraenkel, E Centralbl f Bakteriol, 1893, xiii, 13, Ueber Gasphlegmonen, Hamburg and Leipzig, 1893, L Voss

germ was probably seen by Rosenbach as early as 1884 in gaseous gangrene, but he did not realize its significance. Since the work of Welch and Nuttall,<sup>4</sup> Fraenkel<sup>6</sup> and others, the great majority of cases of emphysematous gangrene have shown the presence of *Bacterium welchii*, or as it is called in France, *Bacillus perfringens* (Veillon, Zeuber), or bacillus of Achalme. From time to time, however, cases of emphysematous gangrene due to aerobic organisms have been described. According to some observers, such cases occur only in diabetics, others assert that the condition may arise without any evidence of sugar being present in the tissues, and it is in support of this latter view that I wish to present the findings in this case.

#### REPORT OF CASE

The patient was a man about 50 years old, brought to the university hospital at Ann Arbor in very bad condition. He had suffered from a retention of urine, and his family physician, having no regular aspirating set or similar apparatus, had punctured the bladder suprapubically by means of a large trocar about a quarter of an inch in diameter. When the patient was brought to the hospital there was a slight discharge of pus from the meatus and also from the wound made by the trocar. There was a small amount of gas in the tissues about the wound and a few gas bubbles could be expressed from the meatus along with the pus. The gangrenous condition rapidly grew worse and the gaseous distention of the adjacent tissues became more and more marked. There was not, however, the coppery hue seen in infections with *Bacterium welchii*. The patient died about seventy-two hours after his admission to the hospital. Post-mortem examination showed purulent peritonitis with gaseous gangrene of the tissues about the bladder. Frequent examination of this patient's urine showed sugar to be absent at all times.

#### MICROSCOPIC EXAMINATION

At the post-mortem examination pus was taken from the meatus, seminal vesicles, and peritoneum near the bladder. Smears were made and plates pouled and incubated at 37° C. The smears showed the same forms described in the cultures. Both aerobic and anaerobic methods of cultivation were employed, the latter being obtained by Novy jars with pyrogallate method of oxygen absorption.

The aerobic plates of pus from the seminal vesicles and peritoneal exudate showed, in twenty-four hours, large numbers of round, moist, grayish-white colonies which spread rapidly and which showed darker center with clear outer zone, rather regular in outline with no marked venation. In the case of the pus from the meatus there were also found two other organisms, one identified as a *Staphylococcus pyogenes albus*, the other a short motile bacillus later identified as a *proteus* which showed no pathogenic effect on laboratory animals.

In the anaerobic cultures large numbers of colonies similar to those described for the aerobic plates were found in thirty-six hours. No other germs developed, and on subsequent tests these organisms proved identical with those from the aerobic plates.

A culture from each source was studied and various subcultures made, all of which showed the same characteristics. Cultural methods described by Corner and Singer<sup>7</sup> and Dudgeon and Sargent<sup>8</sup> were employed, and the laboratory strain

7 Corner and Singer Tr Path Soc London, 1901 iii, 42

8 Dudgeon and Sargent Tr Path Soc, London, 1904, iv, 107

of the colon bacillus was carried through the same procedures as the organism under investigation. The following are the most important characteristics of the germ.

*Morphology*—A very short bacillus, almost coccus like in shape, especially in anaerobic beef-tea culture, where short threads of three or four seem to predominate. The same appearance was noted by Chavigny<sup>9</sup> in working with his organism. On agar streak under aerobic conditions the bacillus form was more common, diplobacilli being frequently seen but no long threads.

*Motility*—Actively motile when first isolated, but this soon became a rather sluggish movement under artificial cultivation.

*Spore formation*—None observed.

*Oxygen Requirements*—Facultative anaerobe.

*Staining Reaction*—Stains well with ordinary aniline dyes but does not stain by Gram's method.

*Thermal Death-point*—Killed by five minutes' exposure to 60 C. Two tenths per cent carbolic acid did not inhibit the growth of the organism.

*Cultural Characteristics*—Beef Tea. Very turbid in twelve hours with stringy white deposit on bottom of test-tube, no scum on surface. After several days the same picture was seen; at no time was there any scum found on the surface of the liquid.

Litmus Milk. Tube showed early reduction of litmus and rather slow coagulation of casein. In some tubes this was not present until the third or fourth day, but in all cases coagulation had occurred by the seventh day. There was no subsequent peptonization of the casein in ten days.

Glucose Litmus Gelatin Stab. A few of the tubes showed gas bubbles in twelve hours all were well split up by the end of twenty-four hours. No liquefaction of the gelatin in ten days.

Plain Gelatin Stab. Good growth in twenty-four hours with small amount of surface spread, this becoming more marked later on. Some tubes showed gas formation, others did not. No liquefaction in ten days. Strains which showed gas production after cultivation on laboratory media for some generations lost this power to a considerable extent.

Agar Streak. Moist, slightly spreading growth, somewhat raised in center.

Glycerin Agar Streak. No difference except that growth appeared to be somewhat more rapid.

Glucose Agar Streak. Medium fragmented in twenty-four hours.

Blood Serum. Thick, moist, white growth, no liquefaction in ten days.

Potato. Growth thick, raised, moist and yellow-brown in color.

Neutral Red Gelatin Containing Glucose. This medium was fragmented in twenty-four hours with subsequent gradual discoloration of the red. After seven to ten days decoloration was complete. No liquefaction.

Neutral Red Agar Containing Glucose. Abundant gas in twenty-four hours, medium decolorized completely in three to four days.

Litmus Cane-Sugar Agar Shake. Reduction of litmus with the formation of a few gas bubbles.

Litmus Mannite Agar Shake. Abundant gas in twenty-four hours with subsequent reduction of the litmus.

Capaldi and Proskauer<sup>10</sup> Medium No 1. Good growth and acid production in twenty hours.

9 Chavigny Ann de l'Inst Pasteur, 1897, vi, 860

10 Capaldi and Proskauer Ztschr f Hyg, etc, 1896, xxiii, 452

Capaldi and Pioskauer<sup>10</sup> Medium No 2 Slight acidity in twenty hours This same test was given by several of our laboratory strains of *Bacillus coli*

Indol Well developed in cultures five to eight days old

The above cultures were grown at incubator temperature with the exception of the gelatin stabs, which were grown at the temperature of the room Growth was abundant in both cases

Sugar-free beef tea plus 1 per cent glucose, lactose, saccharose and mannite were tested, and in all cases fermentation was shown In case of saccharose this fermentation was slight but undoubtedly present The fermentation tubes were incubated for twenty-four hours before inoculation The aerogenic power on all these media was markedly decreased after the germ had been grown for several generations on the laboratory media In all cases control tubes of the media were used and cultures from our laboratory strains of the *Bacillus coli* tested along with the germ under investigation The germ in this case differed from our stock culture in being more active in reduction of litmus and less active in its action on saccharose in the fermentation tube

The above characteristics place the germ in the colon bacillus group variety alpha of Theobald Smith,<sup>11</sup> or *Bacillus coli communis* of Durham<sup>12</sup>

*Pathogenesis*—Intraperitoneal and subcutaneous inoculations of the pus were made but there was no effect except in one case, which is discussed later on On inoculation of a pure culture into a small white rat intraperitoneally, death followed in eighteen to twenty-four hours and the post-mortem examination showed a purulent peritonitis The bacillus was isolated from the heart blood in pure culture The same result was obtained in the case of guinea-pigs One guinea-pig inoculated subcutaneously with pus developed a necrotic burrowing area beneath the skin but no gas bubbles were found *Staphylococcus pyogenes albus* and *Bacillus coli* were recovered from the lesion When this germ was inoculated subcutaneously there appeared in the course of twenty-four to forty-eight hours a large red edematous swelling which subsequently healed without any necrosis or gas bubbles appearing Animals all recovered from subcutaneous inoculations

In animals inoculated subcutaneously with a mixture of our germ and the *Staphylococcus pyogenes aureus* there was more or less pus formation but no gas production Animals recovered

Welch's<sup>13</sup> test for the aerobic variety of his anaerobic bacillus was also tried but with negative result

#### REVIEW OF LITERATURE

In 1900 Welch<sup>13</sup> discussed most thoroughly the whole literature on emphysematous gangrene, and stated that in his opinion *Bacillus coli* could produce gaseous gangrene only in diabetics He states, further, that he thinks those who report such cases of colon gangrene with gas formation have confounded the organism with what he calls the aerobic variety of his bacillus This aerobic germ was isolated from two cases at the Johns Hopkins Hospital by Lanier,<sup>14</sup> and he considers it identical with an organism obtained from garden soil by Sanfelice,<sup>15</sup> and called by

11 Smith, T Am Jour Med Sc, 1895 cx, 283

12 Durham Jour Exper Med 1901, v, 363

13 Welch, W Bull Johns Hopkins Hosp, 1900, xi, 185

14 Lanier Bull Johns Hopkins Hosp 1900, xi, 185

15 Sanfelice Ztschr f Hyg, etc, 1893, xiv, 339

the latter *Bacillus pseudo-cdematis maligni*. Sanfelice was working with the *Bacillus cdematis maligni* at the time, and observing the similarity he named the organism isolated by him as above. Klein<sup>16</sup> found a similar organism in garden soil. Sanfelice in the course of his investigation examined soil, dust and feces from many sources, and found his *Bacillus pseudo-cdematis maligni* in a large number of the specimens examined. All of these aerobic organisms, however, should be classed as members of the ubiquitous colon group.

Muscatello and Gangitano<sup>17</sup> report five cases of emphysematous gangrene, in two of which they consider the *Bacillus coli* to have been the etiological factor. These authors state that in one of these two cases *Streptococcus pyogenes* was found associated with the *Bacillus coli*, while *Proteus vulgaris* of Hausei was found in the other. They consider that the organism described by them is a variety of *Bacillus coli* which can produce gas in the tissues, but they observed that this power was rapidly lost when the organism was grown on the ordinary media. They consider the bacillus isolated by Sanfelice to be identical with their own, but they do not consider the organism as a new species, rather as a strain of *Bacillus coli*, differing somewhat from the classical descriptions of that organism. They say, "We cannot agree with those observers, Chiaia, and Hitschman and Lindenthal, who assert that the *Bacillus coli* has the power of producing gas only in diabetics." Experimentally, Muscatello and Gangitano were able to produce gaseous gangrene by the injection of cultures of their bacillus mixed with a strain of the proteus. Clinical proof of their statements is afforded by their two cases in which no sugar was present in the urine and in which both patients recovered, for when diabetics suffer from such an infection the prognosis is grave, "simple infections running a progressive course marked by a necrotic character."

Chavigny<sup>9</sup> in 1897 reported a case of emphysematous gangrene marked by comparatively slow progress, in which an organism was found that he considers identical with the organism of Sanfelice. But Chavigny states that he considers it to bear a close relationship to *Bacillus coli*, although not identical with the strain which he used as a control and with which he was unable experimentally to produce gaseous gangrene. In the case of his organism, however, he was able to accomplish this by inoculations of his organisms plus *Staphylococcus pyogenes albus* or plus the toxin of *Staphylococcus pyogenes aureus*.

16 Klein Centralbl f Bakteriol, 1895, viii, 137

17 Muscatello and Gangitano Munchen med Wehnschr, 1900, xlvi, 1303

Evans<sup>18</sup> and Heaton<sup>19</sup> report cases of emphysematous gangrene due to *Bacillus coli*, but the information given is too meager to be of value in a critical discussion of the subject.

Dudgeon and Sargent<sup>8</sup> report a case of gaseous gangrene in which very thorough bacteriological tests were made and in which the patient had at no time showed any sugar in his urine. Aerobic and anaerobic plates were made, and under both conditions *Bacillus coli* was found. The aerobic plates also showed the presence of *Staphylococcus pyogenes albus*. Dudgeon and Sargent give in detail their experiments, the majority of which were repeated with the germ considered in this paper. As in our case, they were unable to get gas in the tissues of experimental animals either with pure or mixed cultures. They also performed the test which Welch considers essential for the identification of both his aerobic and anaerobic gas bacilli and with negative results. They also performed the same test with an organism described by Corner and Singer<sup>7</sup> as identical with Sanfelice's *Bacillus pseudo-edematis maligni* with a negative result. These results strongly corroborate the contention of Muscatello and Gangitano that in all these cases of gaseous infection due to an aerobic organism we are merely dealing with a very active gas-producing strain of the colon bacillus, this aerogenic power being rapidly lost.

Van Dungern<sup>20</sup> isolated from a case of gaseous gangrene the germ which he considers as the *Bacillus coli*. He was unable to produce gas in the tissues of experimental animals. His patient's urine was free from sugar.

Roth<sup>21</sup> reports a case which he says to have been due to *Bacillus lactis aerogenes*. He doubtless confounded the germ isolated in this case with the germ of the colon group proper. Roth also cites a case of colon gangrene reported by Margarrucci, but details of this case are lacking.

Directly in opposition to the views of Muscatello and Gangitano,<sup>17</sup> Dudgeon and Sargent,<sup>8</sup> and others, stands the work of Chiari,<sup>22</sup> Welch, Lindenthal and Hitschman,<sup>23</sup> and Corner and Singer.<sup>7</sup> All of them assert that the *Bacillus coli* can produce gas only in the tissues of diabetic patients. Corner and Singer<sup>7</sup> go a step farther and assert that the organism isolated by them, as well as those organisms isolated by several other

18 Evans Lancet, London, 1898, i, 224

19 Heaton Lancet, London, 1899, i, 398

20 Van Dungern Munchen med Wehnschr., 1893, vi 747

21 Roth Centralbl f Bakteriol., 1899, xxv, 706

22 Chiari Prag med Wehnschr., 1893, i, 1

23 Lindenthal and Hitschman Centralbl f Chir., 1899, xxvi, 5

observers were in reality what they call *Bacillus edematis aerobius*, the latter being identical with *Bacillus pseudo-edematis maligni* of Sanfelice.

Westenhoefer<sup>24</sup> reports two cases, in one of which sugar was present in the urine, no information being given on this important point as regards the second patient. He considers the gas formation in all cases to be a secondary action on necrotic and dead material, and that the *Bacillus coli* acts as a pure saprophyte in such cases. A similar view is held by the majority of men in regard to the infections with *Bacillus aerogenes capsulatus*, Fraenkel being one of the few men who consider *Bacillus aerogenes capsulatus* as an invader of the body in normal conditions of health. Rodella<sup>25</sup> considers that the question as to the ability of *Bacillus coli* to produce gas in the tissues of men is not yet settled. He, however, quotes Sandler who asserts that there is a variety of *Bacillus coli* which is able to produce gas in the tissues of man and that without diabetes being present.

For references regarding the chemical and toxic action of *Bacterium welchii* in gangrene and allied conditions the reader is referred to the recent article by McCampbell<sup>26</sup>.

#### SUMMARY

Cases of emphysematous gangrene may be due to anaerobic or to aerobic organisms. By far the most common factor is *Bacillus aerogenes capsulatus*, otherwise known as *Bacterium welchii*, a few cases have been proved to be due to infection with *Bacillus edematis maligni*.

The organism isolated by Lamei, which Welch calls the aerobic variety of his gas bacillus, *Bacillus pseudo-edematis maligni* of Sanfelice, *Bacillus edematis aerobius* of Cornei and Singer and the organism isolated by Klein should all be considered as varieties of *Bacillus coli*. Certain cases, as described above, have shown under careful bacteriological tests that the gas production was due to some variety of the colon bacillus. Examination of the urine of these patients showed them to be free from diabetes.

Medical Laboratory Building, Iowa City, Iowa

24 Westenhoefer Vichow's Arch f path Anat, 1902, clviii, 185

25 Rodella Centralbl f Bakteriol, 1903, xxviii, 735

26 McCampbell Jour Infect Dis, 1909, vi, 537

# AN EXPERIMENTAL STUDY OF THE ANTITRYPTIC ACTIVITY OF HUMAN SERUM

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## INTRODUCTORY

It has recently been asserted by a number of investigators that the antitryptic power of blood serum affords a reliable diagnostic criterion of the existence of cancer. It is the object of the present paper to record the results of a series of observations based on this new method, and to give a critical estimate of the value of these results from a practical and a theoretical point of view.

It has been known for many years that blood serum is capable of inhibiting the proteolytic power of trypsin. First made by Fermi and Pernossi, this observation was at once confirmed by Camus and Gley, Pugliese and Coggi, and in Germany by Hahn, more recent observations by Kolaczek, Bittoff, Muller, Wiens and Opie, established the fact beyond question. Ascoli and Bezzola in 1903 found that the antitryptic power of the serum was notably and constantly increased in cases of croupous pneumonia. Other observers determined a similar increase in other pathological conditions, notably the infectious diseases. In 1908 it was shown by Brieger and Trebing<sup>1</sup> that the increase in the antitryptic power of the serum was so constant a characteristic of malignant disease—whether carcinomatous or sarcomatous in nature—as to be demonstrable in 90 per cent of the cases. They found that the same condition was associated with a number of other diseases characterized by cachexia, including such widely different conditions as pernicious anemia, phthisis, syphilis, arteriosclerosis, Bright's disease, gout and amebic dysentery. In the later publications, accordingly, they speak of the method as the reaction for cachexia—*Kachexie-Reaktion*. They conclude, nevertheless, that the method, when taken in conjunction with the clinical findings, is of great value to the differential diagnosis of malignant disease. Von

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<sup>1</sup> Brieger and Trebing. Ueber der antitryptischen Kraft des menschlichen Blutserums. Berl. klin. Wochenschr., 1908, xlv, 1041, Weitere Untersuchungen, loc. cit., 1908, xlv, 1349, Ueber der Kachexiereaktion, loc. cit., 1908, xlv, 2260

Bergmann and Meyer,<sup>2</sup> who repeated the work, with an altered technic, confirm in the main the conclusions of Briegei and Trebing. They find that there is an increased inhibitory action of the serum, a so-called "positive reaction," in 92.7 per cent of the cases of cancer. They found a positive reaction to be present also in 24.2 per cent of the non-cancerous cases in which they tested the serum. They fail to confirm the theory of Briegei and Trebing that the positive reaction is characteristic of cachexia, inasmuch as it was absent in certain diseases associated with this condition, and present in certain of the normal, well-nourished individuals. They conclude that a "negative" reaction should be held, except in the presence of unquestionable evidence of cancer, to exclude the diagnosis of malignant disease, a "positive" reaction is to be regarded only as confirmatory evidence. Herzfeld,<sup>3</sup> using the technic of Von Bergmann and Meyer, found a positive reaction in 83.4 per cent of the cases of cancer, of which he examined 12, and in 42.5 per cent of the other cases, of which he examined 40. He concludes, therefore, that the positive reaction is of no diagnostic value, while the negative reaction is possibly sometimes of value, in conjunction with other evidence, in excluding the diagnosis of cancer. More recently, a considerable number of publications have dealt with the method, and have practically confirmed the conclusions above summarized (Roche,<sup>4</sup> Hort,<sup>5</sup> Becker,<sup>6</sup> Landois<sup>7</sup>), namely, that the method is of very considerable diagnostic value.

#### METHODS

The methods which have been devised to demonstrate the antitryptic power of serum are of considerable interest. The earlier investigators generally used leucocytes as a ferment and gelatin plates as the object of digestion. These methods are now of little more than historic interest. Mullej and Jochmann introduced the use of Loeffler plates, i.e., of blood serum and glucose bouillon. Marcus found that a solution of trypsin could be substituted for the emulsion of leucocytes. Briegei and Trebing combined these modifications in the following method, the details of

<sup>2</sup> Bergmann and Meyer. Bedeutung der Antitrypsinbestimmung im Blute Berl klin Wchnschr, 1908, xlv, 1673

<sup>3</sup> Herzfeld, E. Beitrag zur Briegeischen Reaktion Berl klin Wchnschr, 1908, xlv, 2182

<sup>4</sup> Roche, M. E. The Antitryptic Content of Blood Serum in Malignant Disease THE ARCHIVES INT MED, 1909, iii, 249

<sup>5</sup> Hort, E. Antitryptic Reaction Brit Med Jour, 1909, p. 966

<sup>6</sup> Becker, G. Der Antitrypsingehalt des Blutes in der Gynecologie Munchen med Wchnschr, 1909, lvi, 1363

<sup>7</sup> Landois, F. Untersuchungen über den antitryptischen Index des Blutes Berl klin Wchnschr, 1909, xlvi, 440

which, as they state, demand exact attention in order to ensure the best results.

The trypsin used is that of Kahlbaum, and should be made up freshly for each test in a 1 per cent solution. The test media are plates of beef serum, the serum should be tested before pouring, and all serum is to be rejected of which the alkalinity is higher than such as to enable 1 cc to neutralize 0.1 cc of decinormal hydrochloric acid. The plates are to be used only after they are several days old, and only those with a perfectly smooth surface are accepted. Blood is taken from the patients three or four hours after eating. One platinum loopful of the serum derived from this blood is mixed with from one to ten loopfuls of the solution of trypsin, giving ultimately ten mixtures of serum and trypsin, the former in constant, the latter in ascending amounts. Of each of these mixtures six or eight loops are transferred to the surface of the plates, of which as many as five are generally required. The plates are then incubated for twenty-one hours at a temperature of 55°C. Every precaution is taken to avoid contamination of the material, and the temperature of incubation almost excludes the growth of contaminating micro-organisms, while it does not interfere with the activity of the trypsin. The results are interpreted in the following manner:

Cases in which the serum is able to inhibit the digestive action of more than five times its own volume of a 1 per cent solution of trypsin are regarded as possessing distinctly increased antitryptic power, or as "positive," cases in which the serum does not equal this strength are regarded as "negative," inasmuch as the average normal serum is competent to inhibit three times its volume, and a considerable proportion even four or five times the volume of trypsin. The highest admixture of trypsin which fails to produce a visible depression, or "dell," on the surface of the plate, is regarded as indicating the limit of inhibitory power on the part of the serum.

In spite of the fact that the method is given with a certain amount of detail, a number of important factors have been omitted, which may best be mentioned here. It is necessary to use about 30 cc of serum for each Petri dish. The plates after being poured are sterilized at 90, 80 and 75° on three successive days. They are then dried by exposure to the temperature of the incubator for one day, and are kept in the ice-chest until needed. The temperature at which the serum and the trypsin are mixed plays as will be shown in the body of this article, a considerable rôle in the reaction, as does also the length of time during which they are in contact before being applied to the surface of the plates. It is advisable, therefore, that these two variable factors be excluded by a technic

calculated to ensure their constancy. In place of a loop as the unit of measurement, I have found it advisable to substitute the use of accurately graduated pipettes, using 0.1 or 0.25 cc of serum in each test, and adding thereto ascending multiples of this amount of trypsin. This variation in technic demands larger quantities of serum, but ensures much greater accuracy and thoroughness of dilution. Of each of the mixtures, a single loop is transferred to the surface of the plates, which are incubated, as described by Brieger and Tiebing. When the technic has been successful, it is very simple to determine by an inspection of the plates an equation between the serum and the amount of trypsin which it is competent to inhibit. Further details regarding the technic and the results of the method will be included in the body of the article.

Bergmann and Bamberg<sup>8</sup> criticized the foregoing method chiefly on account of the laborious character of the technic involved. In their work they substituted the casein method of Fuld and Gross. In this method the digestive action of trypsin is tested against a solution of casein instead of against serum, and the activity of digestion is determined by precipitating the undigested casein at the end of a certain period of incubation by the addition of acetic acid. The reagents employed in the test are a solution of casein, acetic acid, a solution of trypsin and the serum. The casein solution is prepared by dissolving 1 gm of casein in 100 cc of a decinormal solution of sodium hydroxid, with the help of a moderate degree of heat, this solution is made neutral to litmus by means of decinormal hydrochloric acid, and is finally brought up to 500 cc by the addition of 0.85 per cent sodium chlorid. The acetic acid is in a 5 per cent solution in 45 per cent alcohol. The trypsin solution is made by adding 0.5 gm of Grubler's trypsin siccum to 50 cc of a 0.85 per cent solution of sodium chlorid, to which has been added 0.5 cc of a normal soda solution, this solution is then diluted ten-fold with 0.85 per cent salt solution. The final strengths are, therefore, casein in a 0.2 per cent solution and trypsin in 0.1 per cent solution, the serum is made up into a 2 per cent dilution in physiological salt solution. It was found that 0.5 cc of this trypsin when added to 2 cc of the casein and incubated for one-half hour, yielded no precipitable residue on the addition of the acetic acid, 0.4 cc of trypsin, however, yields a slight precipitate, the former amount is, therefore, the minimal quantity necessary to ensure complete digestion of the casein. The antitryptic action of the serum is measured in the following manner. Into each of six test-

<sup>8</sup> Bergmann and Bamberg. Zur Bedeutung d. Antitrypsins im Blute. Berliner Kliniken, 1908, xlv, 1396.

tubes is measured 0.5 c.c. of the 2 per cent. dilution of serum, to each in turn is then added an increasing amount of trypsin, beginning with the above-determined 0.5 c.c., the minimal quantity necessary for complete digestion, and increasing the amount by 0.1 c.c. in each tube of the series, the total quantity in each tube is brought up to 1.5 c.c. by the addition of physiological salt solution. Two c.c. of the casein solution is now added to each tube, and, after thorough shaking, they are incubated for half an hour in the thermostat at 100° F. At the end of this time, the contents of each tube are carefully made acid by the addition of the acetic acid drop and drop, and readings are taken to determine in which tube of the series the first precipitation occurs, in other words, what quantity of trypsin is just sufficient to overcome the inhibitory action of 0.01 c.c. of the serum. Normally, serum inhibits 0.6 c.c. of the trypsin, and cases in which the inhibition does not exceed this value are denominated "negative" (-); cases in which the serum fails to reach this value are denominated --, cases in which the inhibitory power neutralizes 0.7 c.c. of trypsin are denoted as  $\pm$ , serums which neutralize 0.8 and 0.9 c.c. are classed as +, serums of still higher strength as ++. This method has been accepted almost in detail by Herzfeld. It has been criticized by Brieger<sup>9</sup> on the grounds that the subjective element plays a considerable rôle in the estimation of the precipitate, that the acetic acid yields a precipitate with the albumin of the serum employed in the test, that the addition of a slight excess of acetic acid would convert the casein into a soluble acid-albumin, and that the antitryptic action of the serum may be lost in the high degree of dilution to which it is subjected in the test. None of these criticisms offers in the least degree a valid basis of argument against the reliability of the method, which is certainly both more delicate and more manageable than that of Brieger and Trebing. In my own experiments, after a thorough trial of the technic just described, I have found it advisable to make certain changes in the details of the method. I have used casein in 0.1 per cent solution in 0.1 sodium carbonate, trypsin in 0.1 per cent solution in 0.85 per cent sodium chloride, and serum in a 2 per cent dilution. The same quantities of these reagents were used as in the experiments of Bergmann and Meyer, but the trypsin was added last, on the basis of experiments to be described in the body of this article. Incubation is continued for two hours, after which 0.2 c.c. of the 5 per cent acetic acid is added to each tube. These slight alterations in technic, notably the use of half the strength of casein in solution, shift the figures, but do not otherwise affect the results.

<sup>9</sup> Brieger. In report of discussion. Berl. klin. Wehnschr., 1908, xlv, 1415.

## EXPERIMENTAL

It seemed advisable to make certain preliminary experiments in order to determine the conditions which might produce variations in the final results. Two such variable factors were determined, and care was taken to eliminate them in the subsequent work.

The length of time during which the trypsin and the serum are in contact before being added to the casein was found to play a very considerable rôle in determining the amount of digestion undergone by the latter. This was shown by the following experiment.

In a series of six tubes, the usual trypsin solution was added in ascending amounts, from 0.3 to 0.8 cc., to 0.5 cc. of 2 per cent serum. A second (duplicate) set of mixtures was prepared. The contents of the first set of tubes was at once added to six tubes containing 2 cc. of the casein solution, the contents of the second set was added in the same manner, after a delay of fifteen minutes. Both sets were incubated for two hours, after which acetic acid was added. In the first set, precipitation occurred with 0.4 cc. of trypsin, in the second with 0.6 cc. of trypsin. These results agree with a previous observation made by Hedin. In order to eliminate this factor, it was made a rule in the experiments to invert the order of procedure suggested by Bergmann and Meyer, mixing first the casein and the serum, and adding the trypsin last, in rapid succession to all the tubes.

The temperature of the mixtures previous to mixing was found by a series of comparative tests to influence very materially the degree of digestion which occurred during incubation. To obviate this difficulty, the solutions were always made up with water at a temperature of 70° F.

It has always been assumed by Bergmann and Meyer that the results yielded by the serum plate and by the casein methods would be identical, and the close similarity between the statistics obtained by them and by Brieger seemed to substantiate this view. Theoretically, however, it is perfectly justifiable to question this assumption, and it seemed to me a necessary precaution to test a number of serums according to both methods, in order to see whether in each case the results would prove identical. This was done with six serums, which differed considerably in their antitryptic power.

TABLE 1—COMPARISON BETWEEN THE RESULTS OBTAINED BY THE SERUM PLATE AND THE CASEIN METHODS, WITH SIX SERUMS \*

	1	2	3	4	5	6
Serum						
Plate method	1.4	1.6	1.7	1.9	1.5	1.3
Casein method	0.3	0.4	0.5	0.6	0.4	0.3

\* The notation of results is that contained in the previous description of the methods.

The correspondence between the results by the two methods is quite close. It may be regarded as settled, therefore, that the results obtained by one method may be unhesitatingly translated into figures of the other. Consequently, there can be no further reason for adhering to the plate method, as is done by Brieger, in spite of its greater difficulty and intricacy.

The number of serums tested in the present series amounted to 104. Of these 46 came from cases of cancerous new growths, 34 from other diseased conditions, and 24 from normal individuals. 3 cases of facial epithelioma were not included among the malignant diseases, inasmuch as they were all characterized by the absence of those symptoms considered typical of cachexia, anemia and shortening of life. The distribution of results can better be judged from a table than from a detailed discussion of the cases. In Table 2 the number of cases, and the corresponding percentages of the total number in each group of conditions, are stated in the column corresponding to that fraction of a cubic centimeter of trypsin which totally neutralized the inhibitory power of the constant quantity of serum used in the tests, namely, 1 c.c. of a 2 per cent solution.

TABLE 2.—RESULTS IN 104 SERUMS TESTED

	CANCER CASES							
Number	0 1	0 2	0 3	0 4	0 5	0 6	0 7	Total
Per cent	0	0	4	16	18	2	6	46
			9	35	40	4	12	
OTHER DISEASES								
Number		2	10	12	10			34
Per cent	0	7	29	35	29	0	0	
NORMAL								
Number		2	14	8				24
Per cent	0	9	58	33	0	0	0	

Certain striking features of this table are at once evident. It is noticeable that 16 per cent of the cancer cases show inhibition above 0.5 of trypsin, whereas none of the other serums reach this degree of activity. On the other hand, none of the cancer serums fall below 0.3, whereas other conditions average 8 per cent below this figure. The mean of the cancer cases is 0.575, the mean of the other diseases is 0.44. The mean of normal serums is 0.369. Looked at from another standpoint, the table shows that 56 per cent of the cases of cancer fall above 0.4, whereas only 29 per cent of the serums from other diseases belong in this category, and the normal serums without exception fall below 0.5.

These results may be considered either from the standpoint of their diagnostic value or as purely biological phenomena, of interest as bearing

on the general problem of cancer. Diagnostically, it is at once apparent that serums which inhibit more than 0.5 cc. of the trypsin solution are with a very high degree of probability to be classified as of cancerous origin. On the other hand, so small a percentage of cancer cases falls within this group—about 16 per cent—that the advantage derived is of rather small significance in the solution of practical clinical problems. If the inhibition of 0.5 cc. of the trypsin be taken as the criterion, it is found that 56 per cent of the cases of cancer and 29 per cent of other conditions fall together in this wider group. Unquestionably, the overlapping of the cancer serums by those from other diseases in this group appears to be much too extensive to permit of any diagnostic conclusions. On the other hand, if the 10 serums from other diseases falling under 0.5 be analyzed, it is found that 4 came from cases of typhoid, 2 from cases of sepsis and 4 from cases of advanced tuberculosis. It is obvious that these or similar diseases could, in the great majority of cases, be easily identified, and that, therefore, the diagnosis of cancer could with a certain degree of probability be predicated from the determination of this degree of inhibitory activity in a serum, by a process of exclusion of the other conditions which might give rise to similar degree of inhibition. This conclusion, unsatisfactory as it is, agrees substantially with that drawn by Herzfeld. On the other hand, in view of the fact that only a little more than one-half of the cancerous serums evince this degree of inhibition, it is clear that a lower degree of inhibition—a so-called “negative result”—cannot be interpreted in the slightest degree as evidence against the existence of cancer. If, however, a serum falls below 0.4, there is a probability of 90 per cent that it does not belong to a case of cancer.

The conclusions which may be drawn from the determination included in this series agree in some particulars with those of the German observers, while they differ in others. In the first place, it appears that Bergmann is correct in objecting to the description of the reaction as characteristic of cases of cachexia. A considerable number of the cases of cancer which possessed an inhibition of 0.5 were not in the least cachectic, and the same holds true of several of the serums from other diseases falling in the same group. On the other hand, some of the serums evincing a lower degree of inhibitory activity were taken from distinctly cachectic individuals.

The distribution of the cases differs somewhat markedly from that determined by Brieger and by Beigmann, since in the present series the percentage of cases of cancer showing a high degree of inhibitory activity is considerably smaller, while the percentage of other diseases is considerably larger than those found in the earlier observations. The figures,

however, compare very satisfactorily with those found by Herzfeld. The differences are probably attributable in part to certain differences in technic, but chiefly to a different selection of cases, inasmuch as the controls of the present series were chosen, in very large part, from such diseases as are known to give an increased antitryptic index, namely, the infectious conditions.

Judging the reaction from the standpoint of its purely theoretical interest, it must be admitted that the data are unfortunately not of a character to permit of any very fundamental deductions. In the first place, it is apparent that increase in the inhibitory value of a serum is not at all exclusively characteristic of cancer, and in the second place that a considerable number of advanced cases of cancer do not evince any such increase. A comparison of the mean value of cancer serums, 0.515, with those from other diseases, namely, 0.44, indicates that the increment in cancer as compared with other diseases is a matter of degree rather than of kind. On the other hand, it must be admitted that this difference, although simply and solely one of degree, and not of kind, is a very striking characteristic of more than half the number of cases of cancer, while it is entirely lacking in normal individuals, and is present in other conditions generally as an accompaniment only of very severe and serious general infections. In cancer, it may be present before there is any cachexia or marked impairment of the general health. The explanation of this phenomenon is one which must be considered of great interest in its bearing on the influence exerted by the cancerous growth in its host, the human patient.

As is now fairly well understood, this problem is second in interest only to that concerning the origin of the disease itself. The cause of a great part of the distress of malignant disease, and in a large proportion of cases the direct cause of the fatal outcome, or of susceptibility to the intercurrent *causa mortis*, is the anemia, weakness and cachexia caused by the neoplasm. The nature of this influence exercised by the growth on the general economy is, however, entirely obscure. While certain investigators attribute these effects to a soluble circulating toxin (Leyden<sup>10</sup>) secreted or produced by the growth, others absolutely deny any such effects and trace the general deterioration directly to the local disturbances of nutrition produced by the mechanical conditions of the growth. They assert, in other words, that malignant tumors cause disturbances of nutrition only to a degree which would be exactly paralleled by benign tumors occupying the same spatial relationship (Blumen-

10 Leyden. In discussion. *Deutsch med Wehnschr*, 1904, xxx, 1486.

thal<sup>11</sup>) Unquestionably, the existence of such a change in the serum as that denoted by the increase of its antitryptic power in cases of cancer has an important bearing on this general problem, and it is of importance that it should be properly understood.

For a number of reasons, however, a satisfactory explanation of the phenomenon is at the present time impossible. In the first place, it does not seem to have been as yet appreciated by any of those who have dealt with this problem that they are not actually, as they are apparently, measuring the antitryptic value of the serum in this reaction. Some years before the antitryptic reaction was discovered, it was shown by Delezenne and Pozerski, and by Hedin,<sup>12</sup> working with different methods, that serum contains not only an antitryptic element, but also a tryptic (or trypsin-like) ferment. The former is contained in the albumin fraction of the serum, the latter in the globulin fraction. The same conditions have been found to maintain of a rennet-like ferment, and of antirennin, which exist side by side in the serum of the horse. The interpretation of these facts offers certain difficulties from a theoretical standpoint, but the facts themselves seem to be very definitely established. It follows, therefore, that the antitryptic reaction is a measure, not of the amount of antitrypsin in the serum, but of the balance between trypsin and the antitrypsin which the serum contains. The increase in the inhibitory activity of a serum might conceivably mean that the antitrypsin had remained constant and the trypsin had diminished, or that both had increased, but the antitrypsin to a greater extent, or that both had diminished, but the trypsin to a greater degree. It is apparent, therefore, that the present methods reveal only the most elementary data regarding the amount of antitrypsin in the serum.

In the second place, although the reaction has been very generally called an "antitryptic" reaction, there is no valid reason at the present moment for so regarding it. It is antitryptic in the sense that it measures the inhibition of tryptic activity, but not necessarily in the sense that it measures the amount of antitrypsin or antibody to trypsin. In the same way all human serums to some extent inhibit the hemolytic effect of saponin, it would, however, be entirely unjustifiable to argue from this fact to the existence of an "antisaponin". It is, however, a matter of very considerable importance in the interpretation of the "antitryptic" value of serums to determine whether or not these values are to be regarded as attributable to the presence of varying amounts of true "antitrypsin".

11 Blumenthal, E. Untersuchungen, etc. Verhandl d Komm f Krebsforsch Deutsch med Wehnschr, 1904, xxx, 1483

12 Hedin, S G. Biochem Jour, 1906, 484, Antitryptic Action of Serum Albumin. Jour Physiol 1904, 391

The assumption that such is actually the fact has led to the formulation of two theories of the mode of origin of this antitrypsin. By those who consider the increase in antitryptic value as fairly characteristic of cancer, its presence is explained as a protective reaction to the occurrence of a circulatory trypsin, or trypsin-like ferment, derived from the cancer. That such ferments occur in considerable quantities in cancer has been amply demonstrated by Buxton and Shaffer.<sup>13</sup> By another set of investigators, notably Wiens and Schlecht,<sup>14</sup> the antiferment is interpreted as a specific reaction to the presence of a circulating trypsin of the same character, freed, however, by the disintegration of the polynuclear leucocytes, which are well known to contain such a ferment. These investigators believe that there is a very distinct relationship between leucocytosis and the degree of antiferment activity, and they explain on this basis the occurrence of the reaction both in cancer and in certain infectious conditions. Plausible as this theory appears, especially when illustrated by parallel curves of leucocytosis and of antitryptic activity, it is beset by certain very material difficulties. It is, for example, very difficult on this basis to explain the fact that in rabbits the leucocytes possess practically no tryptic power, or at the best a very slight degree, while their serum has a notable degree of antitryptic activity; in dogs the conditions are reversed. It is evident, therefore, that before any attempt can be made to explain or interpret the increased antitryptic activity of serums in certain conditions of disease, notably cancer, it is imperative to determine the character and the cause of this activity. It is not permissible to assume that it is due to the presence of an antitrypsin. It is perfectly conceivable that this form of activity of serum is simply an accidental function of the serum globulin, and that it varies in proportion as this varies, in which case it would belong in the same category as the "antisaponin" activity of the serum. At all events, until these crucial questions are settled, it is hardly reasonable to expect any further advance in the interpretation of the interesting biological phenomenon which forms the subject of this paper.

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13 Buxton and Shaffer Enzymes in Tumors Jour Med Research, 1905, new series, VIII, 543

14 Wiens and Schlecht Die Beziehungen der Leukocytose zur Antifermentreaktion d' menschlichen Blutes Deutsch Arch f klin Med, 1909, LCVI, 44

## SOME CASES OF LOW TEMPERATURE

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In the course of the medical work of this institution, there have been found not infrequently, patients whose temperatures are too low to be registered by the ordinary clinical thermometer. Observations with crude substitutes in one or two cases showed that surprisingly low temperatures were reached. In order that these cases could be properly recorded, special thermometers were procured, reading to a very low point, and an order issued that in all cases in which the temperature was too low for the ordinary instrument, one of the special thermometers should be obtained and a physician on the service should control the readings by personal observation.

Various errors may enter into such work, as follows:

1 Inaccurate instruments. The instruments used are standardized only between 95 and 110 and had the ordinary certificate of accuracy. The lower readings were not tested. One of the instruments used, however, has been sent to the Bureau of Standards, Washington, and their report shows that the average error is  $+0.25$  degrees.

2 Too short exposure to the body temperature to obtain proper registration. The physician's observations should control this point. Ten minutes in the rectum is our rule in this class of patients.

3 Inaccurate readings. The low temperature should be occasional and inconstant, were this factor of importance.

4 The condition of the rectum. It is almost a routine procedure to give cleansing enemas in our low-grade cases in the sick ward, so great are the dangers from constipation. These enemas are naturally hot and should tend to raise the temperature.

5 These cases have occurred at intervals in several different services. This eliminates to some extent the personal equation, in that similar observations have been made by several different physicians and nurses.

6 The regular course of the fall is proof of the general accuracy of the work, as the curve would be irregular, were the low temperature due to any of the sources of error above cited. There are two cases presented below in which the course of the temperature is quite irregular, but in these, the readings check one another during the rise and fall.

It is with some hesitation that I submit these cases. Of late, I have used every opportunity to question institutional people on this subject, and my statements have been met at times with lifted eyebrow or open skepticism. There are, however, occasional reports of such conditions in the literature. Osler<sup>1</sup> quotes a case of acute alcoholism, in which the temperature on admission was about 75 and ten hours later had risen to 91. Ziegler states that complete recovery has been observed in man after reduction of the body temperature to from 75 to 86 F.

There are numerous cases in our records in which temperatures of 94 to 96 F are recorded, but these have not been included in the present report. There were 18 cases which seemed worthy of note.

CASE 1—Patient, E. C., No. 1767, an epileptic idiot, female, admitted March 1, 1905, aged 14. On December 12 it was observed that she looked ill and she was put to bed. Her temperature was found to be 91.2, pulse 70, respirations 18. She groaned as if in pain. Head and lower extremities strongly flexed. Increased vesicular breathing. Abdomen rigid, recti stood out distinctly, tympanitic, pressure caused pain. Later in the day the temperature was below 90 per rectum, the thermometer registering no lower.

The following day the temperature rose to 95 and she vomited twice, the first material having a fecal odor and the second that of the ordinary stomach contents. At the end of the day she was much weaker and vomited again. She died at midnight. A temperature four hours previously was not above 90 F. Autopsy showed pulmonary tuberculosis and partial obstruction of the ascending colon.

CASE 2—Patient, S. F., No. 541, female, admitted Jan. 11, 1900, aged 14 years, feeble-minded. In the latter part of 1905 she suffered with enteritis. This improved, but she died of pulmonary tuberculosis. The last day, between 4 a.m. and 7 a.m., the patient's temperature sank from 98 to 92. She died at 11 a.m.

CASE 3—Patient, M. H., No. 2072, female, admitted Oct. 9, 1906, aged 17, fair mentality. On March 4, 1907, she refused her food and in the afternoon was found in a state of collapse, pulse regular but small and weak. Marked pulmonary signs. When first observed, pulse was 120, respirations 30 and temperature 96.2. In the course of four hours the patient died with a temperature of 92.1 F and respirations of 8 per minute. General tuberculosis was found at autopsy, the immediate cause of death being perforation of a tuberculous ulcer of the bowel.

CASE 4—Patient, H. E. H., No. 2025, male, admitted June 21, 1906, aged 61, was quite demented. In November, 1907, the patient had erysipelas. For some time after the patient's temperature was about normal, it suddenly dropped to 95.8 F to return at once to 98.8 F and once again to drop to 89.4 F, after which it again rose to 99.4 F. It continued slightly subnormal for some time, and then was normal with only two sharp drops to 94.2 F and 94.4 F. Later the temperature became rather irregular and dropped in two days from 99.4 F to 89.6 F. Afterward it twice went to 94 F and then ranged from 97 to 98 F, with occasionally 95.5 F to 96 F. Shortly before death it was 95 and rose at death to 98 F. Pulse had disappeared toward the end. Brain showed slight internal hydrocephalus and marked arteriosclerosis.

CASE 5—Patient T. F., No. 897, male admitted at 15, became a dement, remaining in the colony seven years. He gradually declined and was put to bed in the sick ward. The temperature, pulse and respiration were normal but the

1 Osler Principles and Practice of Medicine, 4th ed., p. 380.

patient appeared weak and excited on Nov 11, 1907. On the 17th it was noted that the patient's temperature was subnormal and his body quite cold. The pulse was feeble and he was stimulated by strychnin and whisky and hot-water bottles. The temperature was 79 F and later in the day dropped to 75 F one hour and twenty-five minutes before death, this being the lowest temperature noted. Autopsy showed old tuberculosis, with some active changes, and chronic parenchymatous nephritis.

**CASE 6**—Patient, No 1305, male, admitted Nov 30, 1902, at age of 25, an imbecile Erysipelas in 1904, possible tuberculous abscess of ensiform process, which recurred once in 1905. Ulcer on neck in 1906. He was an idle dement in fair physical condition. Early in 1907 he began to degenerate physically, and on April 20 it was noted that his skin was unusually cool and it was found that his temperature was 95 F, with no pulse at the wrist, dropping to 78 F and rising to about 82 to 83 F at death. There were no pulmonary signs. Respirations ranged

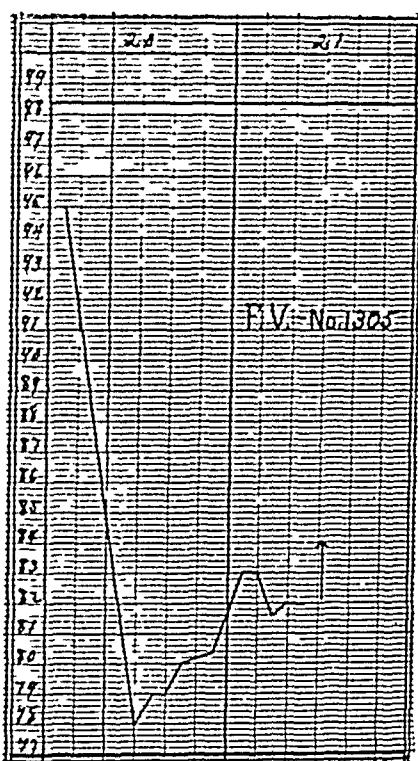


Chart 1—Low temperature in Case 6

from 32 to 42, and two hours before death they were 36. Blood-counts showed marked leucopenia, the average count being between 1,200 and 1,500 whites per c mm. Autopsy showed peculiar shape of tentorium with unusual shape of the posterior part of the cerebral hemispheres, arteriosclerosis of the cerebral vessels, bronchopneumonia and interstitial nephritis, caseated mass in the wall of the right ventricle, to which the pericardium was closely adherent, and fatty liver.

**CASE 7**—Patient, H C, No 1703, female, admitted Dec 12, 1904, aged 41, a dement in feeble physical condition. Several minor infections were noted during the residence at the colony, among them, erysipelas of the leg and thigh, and later bed-sores. The last notes show that there were cough, bronchial breathing, and tympanitic note over the left apex in front, without râles. Pulse weak. At the last the respirations varied from 18 to 30 and the pulse from 70 to 128. The

temperature was 98 F on the 31st, 96.8 F on the 1st, 97.2 on the 2d, 94.2 on the 3d, 97 on the 4th, and death at 92 F on the 5th

CASE 8—Patient, F W, No 434, female, admitted in December, 1898, aged 25, feeble-minded. The later notes report her as a medium-grade imbecile in good general health. On March 10, 1908, she refused her supper and, looking ill, was put to bed. She was slightly stuporous but said she felt well. Temperature 94 F, pulse 48, respirations 22. Extremities, breasts and forehead were cold. Auscultation showed moist râles in the bases and in the right axilla. There was also impaired resonance and harsh breath sounds over the upper front. The

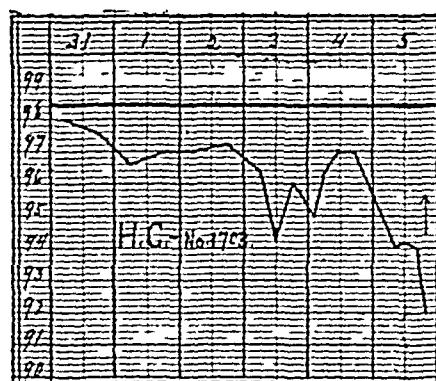


Chart 2—Case 7

patient steadily failed and the last temperature recorded before death was 91 F, pulse 70, respirations 40.

CASE 9—Patient, C C R, No 1860, female, admitted Aug 31, 1905, aged 15, an epileptic idiot. During her residence here there was one attack of enteritis and occasional subnormal temperatures. On November 19 the temperature was 90.4 F. On the 25th, temperature was 91 or below, as this was the point to which the mercury column had been shaken down and no rise had taken place. Bed-sores

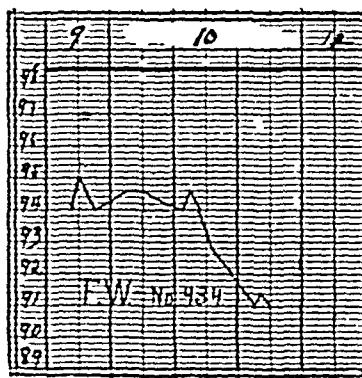


Chart 3—Case 8

were present. Collapse, prostration, emaciation marked her illness. The temperature rose but she died, her temperature at death being 97.2 F. Autopsy showed fibroid phthisis.

CASE 10—Patient F R, No 353, female, admitted July 13, 1898, aged 47, mental status fair. It was stated later in her residence here that she probably had interstitial nephritis. In 1906 there were signs of beginning tuberculosis. On Sept. 21, 1906, she showed slight trace of albumin in the urine with epithelial and waxy casts. There was some edema of the ankles and nausea and headache,

increased blood-pressure, and roughened aortic second sound. Some nausea and vomiting continued. October 23 there was labored breathing. The temperature dropped from 99 F to 90 F, the extremities were cold and the pulse irregular and weak. The urine contained albumin but no casts. The patient's condition gradually failed and she died Oct 25, 1906, the temperature having dropped to 89 F and then risen to 91 F.

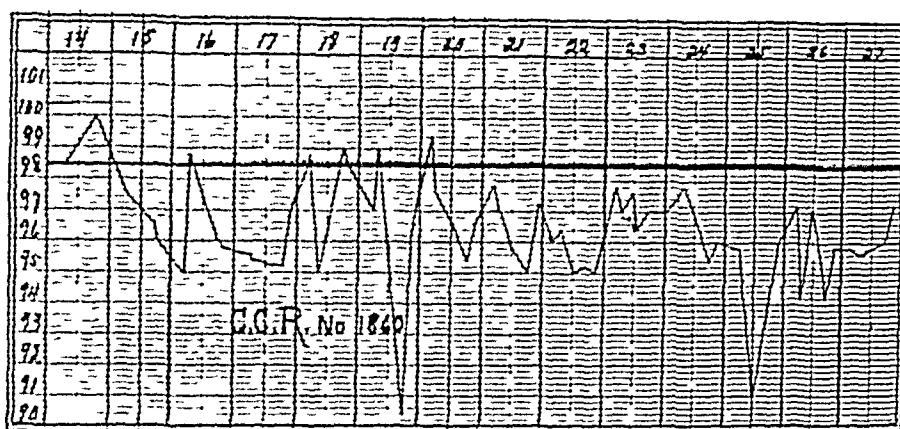


Chart 4—Case 9

CASE 11—Patient, G. L. P., No. 1696, male, admitted Nov 30, 1904, aged 20, mental condition poor. Pulmonary edema and hemorrhage were reported three times. Unfortunately, the later clinical notes are not available, but from personal knowledge the patient had erysipelas and was recovering when the temperature began to go down as noted in Chart 6. The temperature dropped to 90.6 F, rose again to 97.2 F, and shortly before death was 87.5 F.

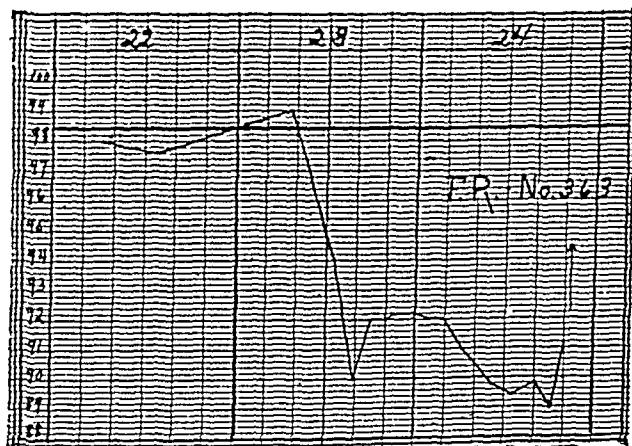


Chart 5—Case 10

CASE 12—Patient, A. C., No. 1854, female, admitted Aug 31, 1905, aged 24. In May, 1907, she complained of pain in the region of the right kidney. This continued and there was slight nausea and vomiting. The temperature was 97 F, pulse 78, respirations 24. She was thirsty and the legs were slightly edematous. There were a few moist rales in the bases of both lungs. Her condition grew worse and the pulse at the wrist disappeared. A urine examination a couple of days

before death showed albumin and sugar, with casts. The condition became steadily worse and the patient died six days after the first complaint of pain in the back, heart-rate being 64. Temperature reached 89.8 F, rising to 95.2 at death. Autopsy showed small nodule of solidification in the upper lobe of the right lung, "probably tubercular." Capsules of kidneys were adherent and the surface was

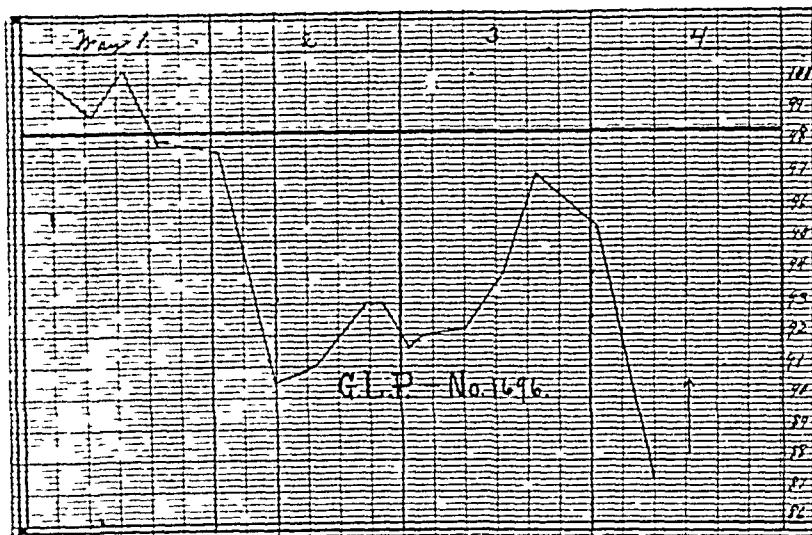


Chart 6—Case 11

pale and mottled. The usual stigmata were not easily seen. Histologic examination showed parenchymatous nephritis, pancreas normal.

CASE 13—Patient, R N F, No 521, male, admitted Nov 21, 1899, aged 12. Mental condition on admission good. During his residence at the colony he deteriorated both mentally and physically. On Dec 1, 1906, this boy had serial

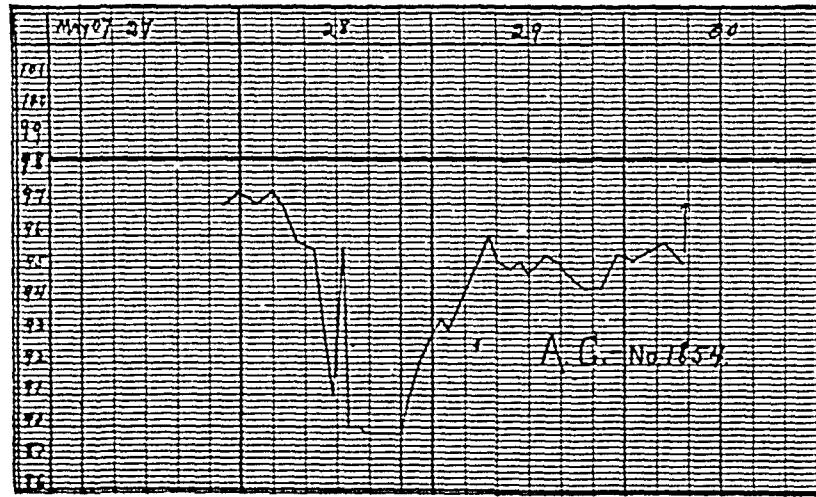


Chart 7—Case 12

seizures, which recurred on the 9th. A subnormal temperature developed a temperature of 95 F being noted on the 1st, 94.5 on the 6th, 78.5 on the 12th and 76 F at the time of death. Pulse was impalpable at the wrist and varied from 72 to 96. Respirations were generally 18.

CASE 14—Patient, G. W. S., No 1804, male, admitted June 19, 1905, aged 10½ years, feeble minded. About a month after admission he developed serial attacks and rapidly sank into unconsciousness and died Aug 2, 1905. The temperature ran an irregular course, reaching 102.4 F at the highest point. As death approached, the temperature fell, reaching at death 81 F. The pulse was rapid, being 114 to 148. Shortly before death the pulse rate was 90 to 96. Respirations on the whole gradually rose, 14 being the lowest and 60 the highest.

CASE 15—Patient, J. B., No 747, male, aged on admission 52. This patient complained, in the spring of 1908, of hematuria, which condition existed in varying degree till death. A tumor was strongly suspected. On April 16, 1909, the temperature dropped to 97 F, following this for a few days it remained approx-

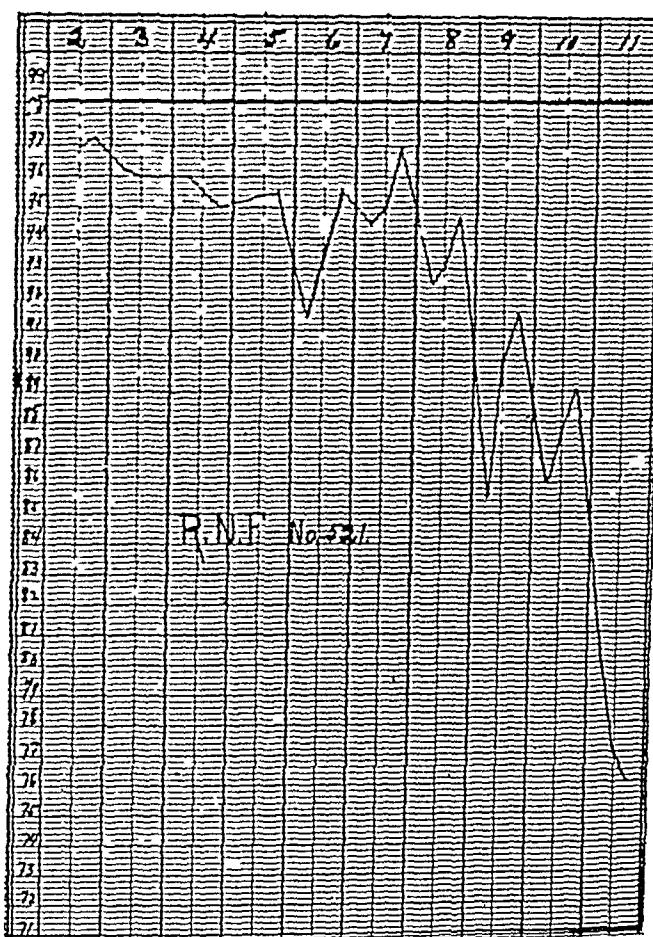


Chart 8—Case 13

imately normal and on the 20th dropped to 96. It remained at this point till the end of the 22d, when it fell to 93-94, and dropped again on the 24th to 91. This continued till the latter part of the 26th, when another drop took place, 87 being reached. On the latter part of the 27th temperature rose to 91, after which a steady fall took place throughout the 28th, ending early in the morning of the 29th, with the death of the patient at a temperature of 73 F. The pulse had gradually become imperceptible at the wrist and was for some time slowed to 60, but rose to 70-80 before death. Respirations not accelerated. Autopsy showed carcinoma of the bladder and ascending pyelonephritis.

CASE 16—Patient, R R, No 1524, female, aged 7 on admission. Previous to this patient's death the temperature ran a distinctly irregular course, being at times subnormal for days and again reaching 103 to 104 F. On March 30 and 31 and on April 1 there was a period in which the temperature varied between 91 and 94. This was succeeded by a speedy rise so that on April 5 the temperature reached 103. A sharp drop occurred and on the 6th 90 was reached. Following this a great irregularity was noted, changes of 91 to 99.8 being noted within six hours. After this period the temperature rose to normal or above and so continued till death. Pulse and respirations were occasionally slowed, a pulse of 48 and respirations of 12 being the lowest. Red blood cells were slightly reduced, white corpuscles about normal. Death was caused by acute dilatation, chronic endocarditis and pulmonary tuberculosis.

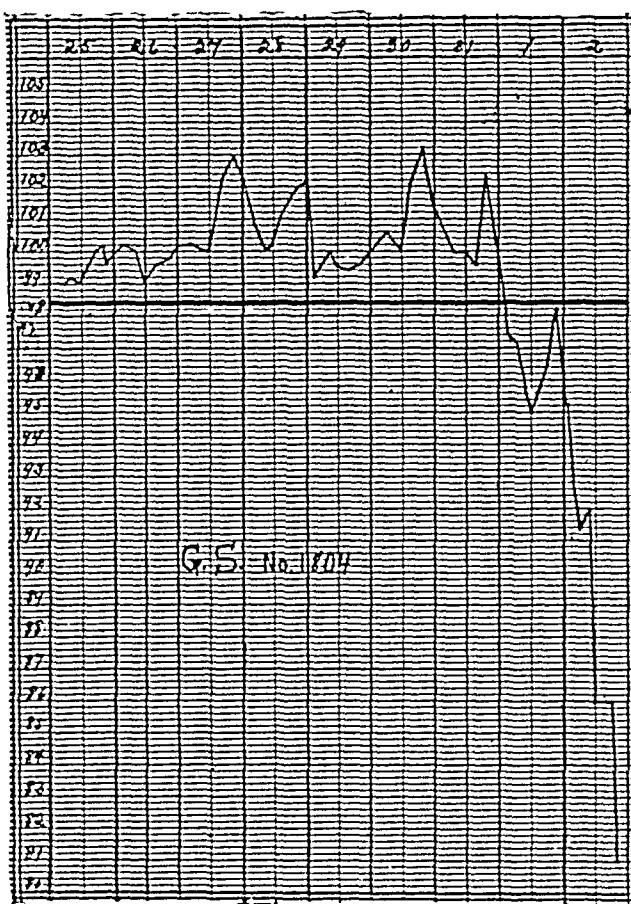


Chart 9—Case 14

CASE 17—Patient F K, No 390 female, aged 56 on admission. On Feb 28, 1905, it was noted that she appeared weak and she was put to bed. There were numerous bruises and an infected toe from which the infection had extended up the thigh. The infected area was incised and dressed. The patient presented symptoms of collapse, the temperature being low, the pulse weak and respirations rapid. On March 2 the lymphangitis was somewhat improved but the patient was in a very weak condition. On the 4th her temperature was reported as subnormal the breathing superficial the radial pulse imperceptible. The temperature during the last few days of her illness was from 90 F to 103 F. The pulse varied from 60 to 96 respiration irregularly accelerated. Autopsy showed brown

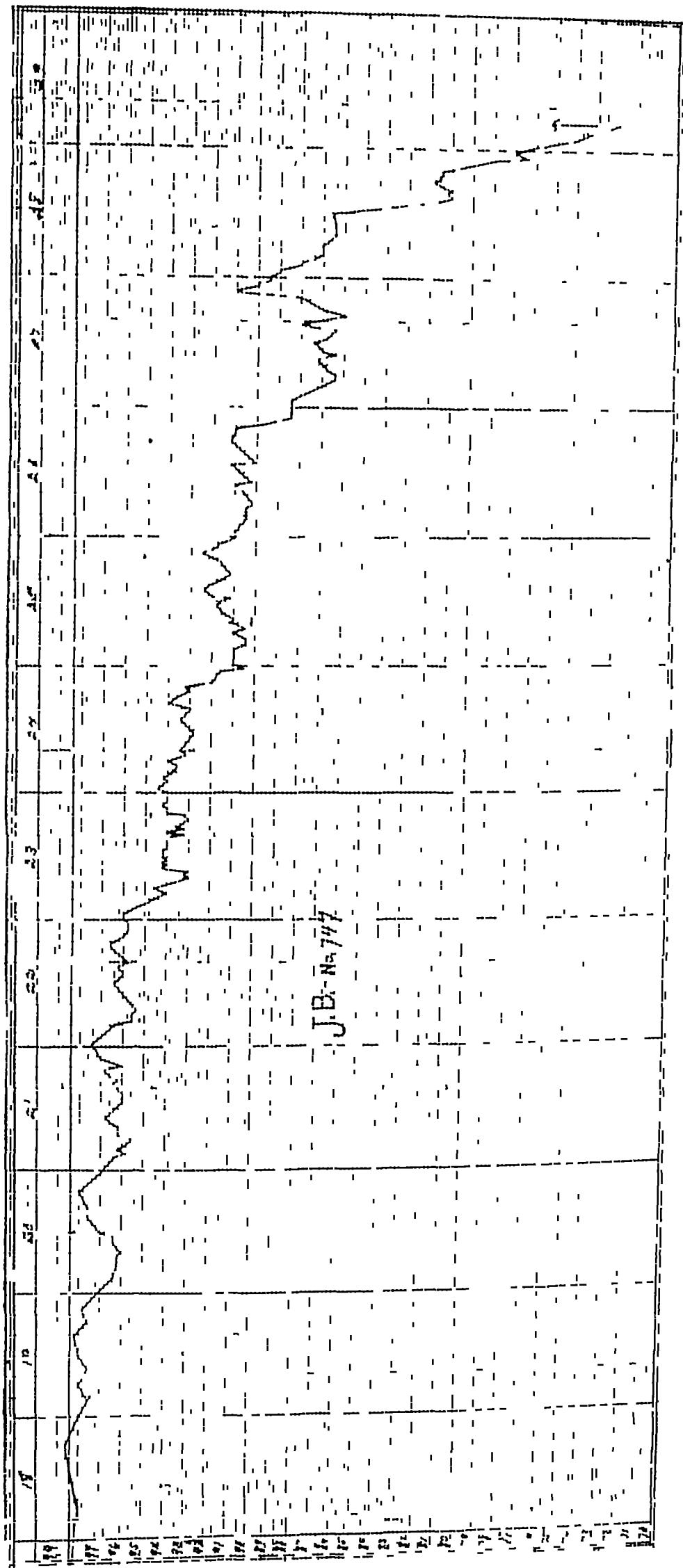


Chart 10—Case 15

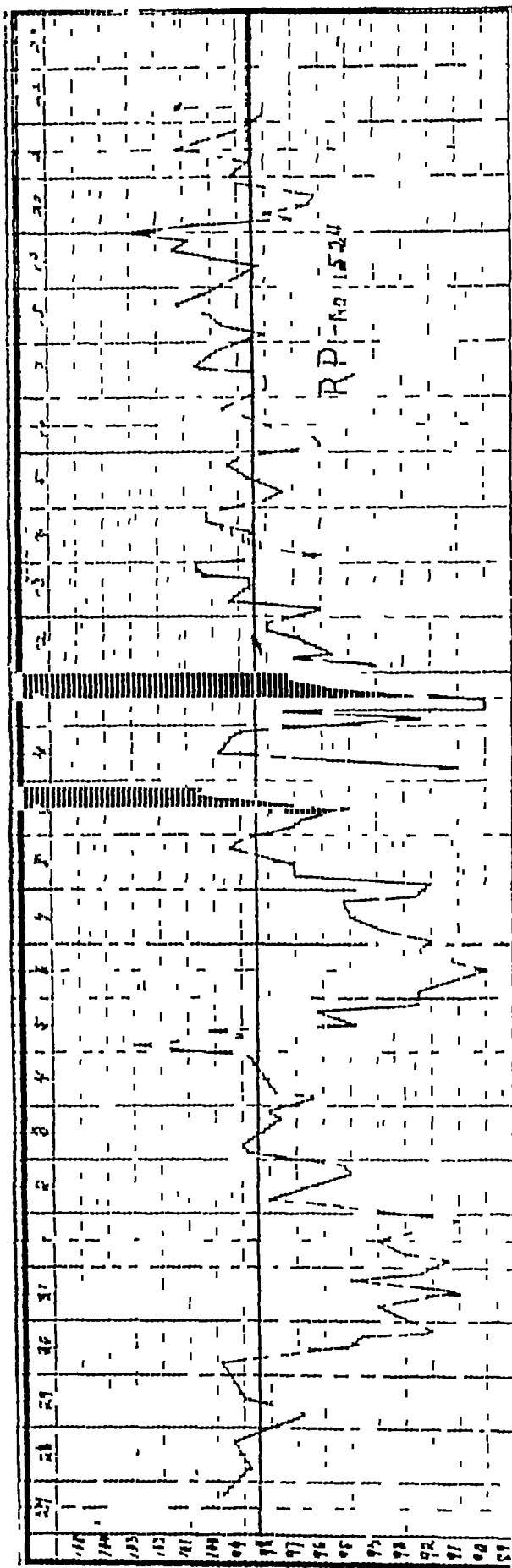


Chart 11—Case 16

atrophy of heart, moderate atheroma, hypostatic congestion of lungs, cirrhotic and fatty kidneys, atypical nutmeg liver

CASE 18—Patient, M A S, No 2523, male, aged 54. There were symptoms in this case suggesting focal disease of brain. For some months a chart showed a temperature varying from 96 to 99 F. Just previous to his death the temperature had been normal or slightly elevated, 100.4 being reported on April 1. Respirations ran 16 to 18 till about six hours before death, rising then to 40, and one hour previously to 9. The pulse failed some twelve hours before death. Heart sounds were faint and distant, finally at times inaudible, at 5.05 a.m. inaudible with stethoscope they did not reappear. Death at 10.02 a.m. with temperature of 81.4 F. White count shortly before death 3,487, reds, 2,925,000, hemoglobin, 90. Urine removed per catheter shortly before death showed numerous hyaline casts but no albumin. Autopsy showed brain tumor.

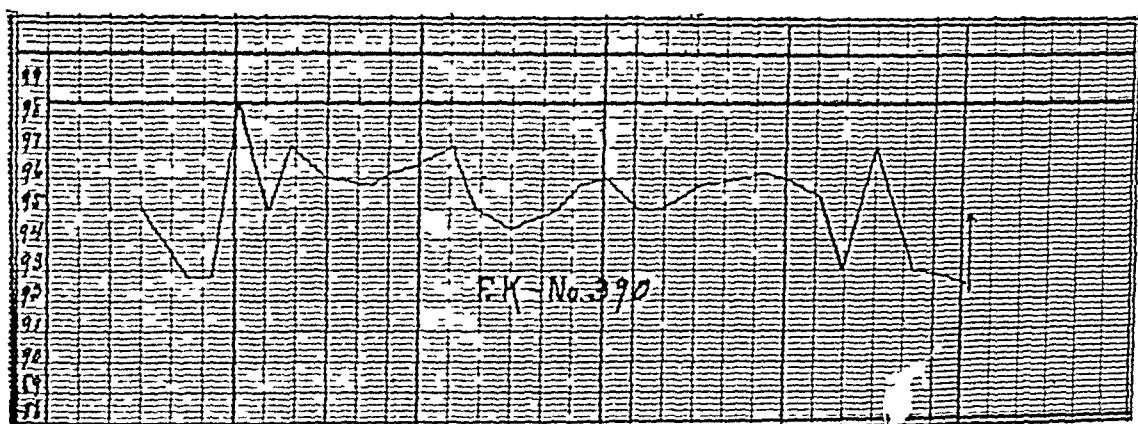


Chart 12—Case 17

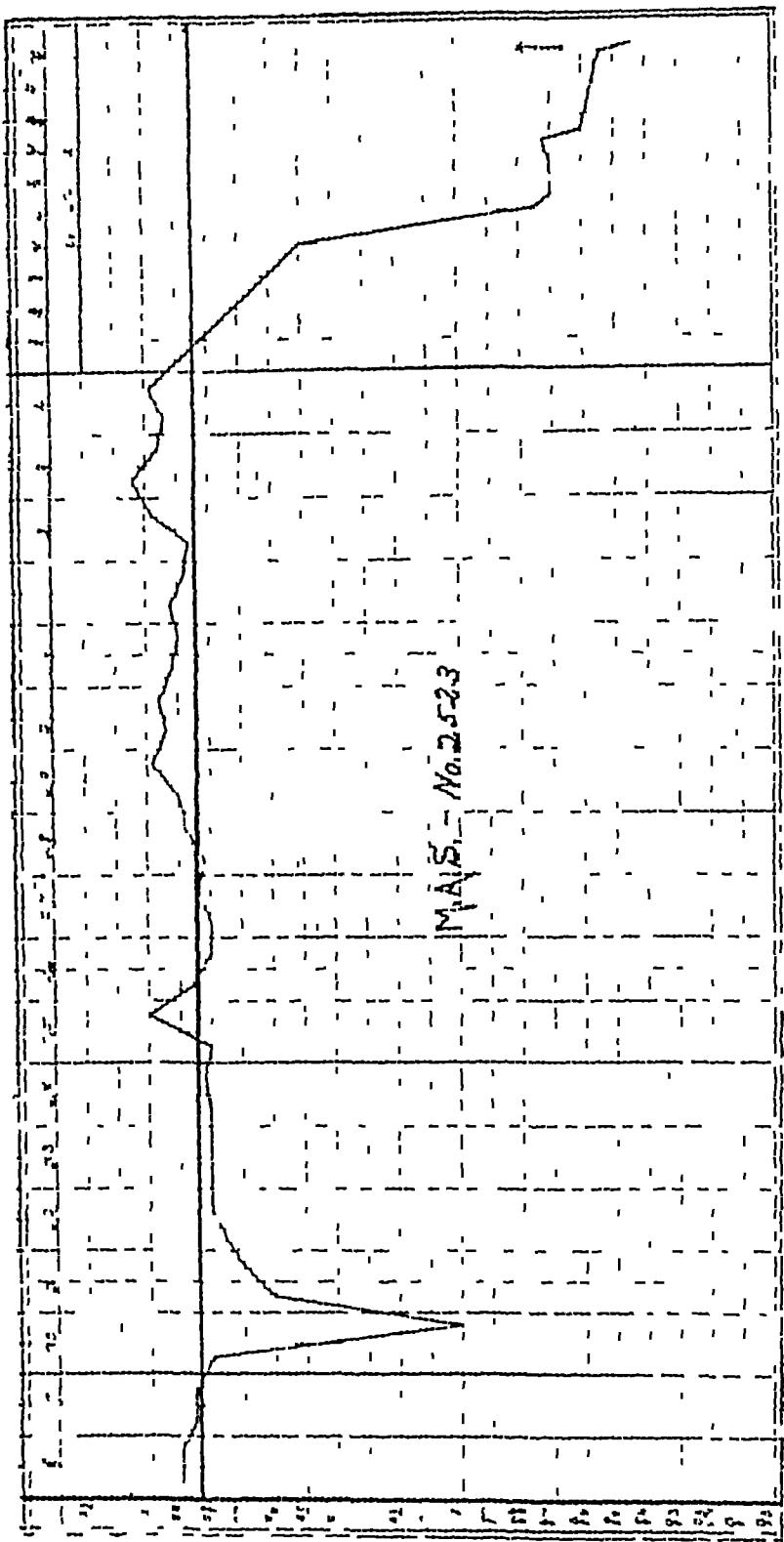
The causes of death in these cases were as follows

Tuberculosis	6
Pneumonia	6
Inanition	2
Acute abdominal conditions (in tuberculous cases)	2
Erysipelas	1
Nephritis	1
Diabetes and Bright's disease	1
Carcinoma of bladder with ascending pyelonephritis	1
Cardiac dilatation, chronic endocarditis	1
Exhaustion	1
Brain tumor	1

In looking over these cases, the following will be noted

- 1 The majority of the patients were of low mental grade
- 2 Some infectious condition was present in almost all the cases. Pneumonia, tuberculosis, erysipelas, and pyelonephritis were among those noted, together with acute abdominal conditions
- 3 Chronic conditions lowering the vitality of the patient were often present
- 4 From the foregoing it will be seen that hypothermia has occurred in low grade patients, suffering with some acute or chronic infection, or with a chronic wasting disease. The low temperature is usually agonal, or preagonal.

Chart 13—Case 18



What rôle is played by the fact that these people were epileptics, with a naturally unstable nervous system, is impossible to state. Theories as to the causation of this condition might be

- Intoxication from absorbed bacterial or other toxins
- Disturbance of the heat regulating mechanism
- Deficient oxidation
- Failure of circulation

It is interesting to recall here that bacterial cellular poisons, as well as some of the poisons to be derived from the protein molecule, cause in experimental animals a fall of temperature quite similar to that seen in some of these cases, especially in Cases 13, 14, 15 and 18. The rapidity is, of course, very different, days being consumed in the human cases here mentioned, whereas hours are consumed in the animals.

In conclusion I wish to thank my co-workers at the Colony for the use of the clinical material from their services and for their helpful suggestions.

## THE PROBLEMS OF EXPERIMENTAL NEPHRITIS

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Our present knowledge of nephritis is the result of the methods of clinical observation, pathological anatomy and experimental pathology, successively applied. By means of the first of these, Richard Bright, in 1827, demonstrated that albuminuria and dropsy had an intimate relation to certain pathological changes in the kidney. Studies in pathological anatomy during the following years led to the differentiation of several types of nephritis, and, finally, to a classification based on morphological alterations. I do not think it an exaggeration to say that clinical observation has added little of essential importance to Bright's original conception of eighty years ago, or that pathological anatomy has added little to Weigert's classification, which has been generally accepted for thirty years. Bright's views, it is true, have been amplified, certain phases of the relation of renal disease to cardiovascular disturbances have been more clearly understood, and much negative evidence concerning uremia and edema has accumulated, but little has been added by clinical methods to our knowledge of the interrelation between a kidney lesion and its manifestations. The methods of pathological anatomy have given a classification, based on careful study of the gross and minute lesions of nephritis, and with these have been correlated in a more or less satisfactory way clinical manifestations and changes in the urine. This most important period of anatomical study began in 1851, with Frerichs, who considered all forms of nephritis as stages of a single process, beginning as an acute nephritis and ending as the small granular kidney, the period terminated with Weigert, who, in 1879, demonstrated conclusively that Frerichs' stages do not represent the successive changes of a single lesion, but are distinct types of nephritis, caused by various injurious substances acting during varying periods of time, and representing the varied reactions of kidney tissue thus influenced. Weigert's view is the one held to-day. More recent studies by improved histological methods have added to our knowledge concerning certain details, especially in regard to the glomerular changes, the sequence of lesions and certain unusual types of nephritis,

but the methods of pathological anatomy offer no promise of an interpretation of the important problems of this many-sided disease.

The application of the experimental method to the study of renal disease is not a recent development. For many years experimental lesions of the kidney have been utilized, and with gratifying results, in the study of the sequence of the histological changes occurring in nephritis. With such studies, essentially anatomical in nature, have been combined, in recent years, investigation by methods which allow an interpretation of changes in function, upon which morphological studies throw no light. Such investigations necessarily demand the methods of chemistry and physiology, and we have witnessed in the past few years the curious spectacle of pathologists turning from the methods in which they were trained to those of the physiologist and chemist in which presumably they had, originally, little or no training. Investigation by such methods is termed "experimental pathology" merely because the pathologist, despising of the anatomical method, has seen fit to adopt them in the study of altered function. It is to such methods that we must look for an advance in our knowledge beyond that which has been possible by the methods of clinical medicine and pathological anatomy, and if the pathologist is criticized, as frequently happens, for appropriating the methods of other sciences and for applying to the field of endeavor thus created the term "experimental pathology," it is sufficient to point out that the physiologist and the chemist, as well as the pharmacologist who shares the same methods, have with few exceptions limited themselves to the field of normal function.

That nephritis has been one of the principal objects of attack by these methods is in part due to the importance of the disease, and in part also to the fact that the kidney lends itself very readily to experimental study. And, moreover, although the results of experimental study may not always be applied to explain disease in man, it must be evident that, owing to the peculiarities of the structure and function of the kidney, results of experimentation with this organ have a very definite application. Thus, some aspects of etiology, the almost specific action of certain substances in picking out certain kidney structures, the character of acute lesions and the relation of these to chronic lesions, questions of repair and regeneration, the matter of cast formation and the source of albumin, are problems which, when elucidated by animal experiments, can readily be transcribed to explain similar problems in human nephritis. But aside from these, the experimental method offers hope, in part already realized, of a solution of the more prominent problems of renal edema, of anuria, the question of the relation of renal disturbances to

hypertension and heart hypertrophy, and the most important, though at present the most hopeless, problem of uremia.

Here I may at once call your attention to the fundamental problem of experimental nephritis, that is, the influence of the glomerulus as contrasted with the influence of the tubule. This enters into all phases of renal pathology, in some partially elucidated, but in most still a matter of doubt and speculation. The dual structure of the kidney is responsible for the difficulty which we have of interpreting the physiology as well as the pathology of this organ. We are familiar with glands in which different types of cell are concerned in the elaboration of different chemical substances, and with those in which cells are modified to produce an internal, as contrasted with an external secretion, but the kidney stands alone as an organ with two widely different structures, having for a common object the elimination of a single fluid representing the products of metabolism. This is not the place to discuss the significance of this structural peculiarity and its bearing on the function of the kidney, though it must be considered in what follows. It may be permitted, however, to point out here that the glomerulus, as has been emphasized by Beddoe, is a structure without analogy elsewhere in the body except, perhaps, in the choroid plexus of the brain, and that the urinary tubule differs from all other gland tubules in its length and complexity. On these peculiarities of structure, coupled with the peculiarities of the renal circulation, depends the power which the kidney has to remove from the blood-stream the fluid and solids which constitute the urine. If we disregard the one synthetic process of which we have positive knowledge, the formation of hippuric acid from benzoic acid and glycine, the essential function of the kidney is one of elimination, with the important feature that the resulting fluid contains all of the soluble components of the blood except its protein constituents and dextrose—in a deficient percentage, it is true, but still the same substances.

If we accept departures from normal elimination as evidence of disturbance of kidney function, the problem of experimental nephritis is to determine the part played in this disturbance by glomerulus and tubule, respectively. This may be done by the use of physiological methods which graphically demonstrate alterations in vascular reactions and by comparing such results with those obtained by chemical study and eventually correlating both with the anatomical changes. By such studies of simple phases of the problem of nephritis, enough has been accomplished to warrant their continuance with the prospect of adding essentially to our knowledge of renal pathology.

The study of experimental nephritis may be expected, however, to do more than explain the sequence and significance of pathological changes. By producing lesions which affect only certain structures as the glomeruli or the tubules, or but certain portions of the tubules, we may expect not only to solve some doubtful points in the physiology of this organ, but also to obtain data of considerable importance to the pharmacologist and therapist, thus bringing the work home to the clinician. As a single example may be given the study of the effect of diuretics on the diseased kidney as compared with their effect on the normal. Our knowledge of the latter action is fairly complete, but we have very little knowledge of the former. The study of vascular dilatation and contraction in the kidney, the elimination of water, the general composition of the urine, the chloride-regulating mechanism and many other points, in distinctly tubular and distinctly glomerular forms of nephritis, which we are now able to produce, should yield practical information of great value. Some information in regard to these matters we now possess, but before it can serve as working knowledge, extensive chemical and physiological studies of various forms of nephritis must be made from the pharmacological point of view.

I have gone somewhat into detail in this introduction, not only for the purpose of demonstrating the value of the study of experimental nephritis, but also for the purpose of showing that the results of such study are of interest to everyone concerned with the problems of normal and abnormal physiology—to the physiologist, the chemist, the pathologist, the pharmacologist and the clinician. And, in order to maintain interest, if it has been aroused, I shall deal briefly with the methods of inducing nephritis, the character of the acute lesions, and the relation of these to chronic lesions, attempting to set forth clearly the types of experimental lesions known as tubular and glomerular. Time thus saved will be devoted to the more interesting questions of altered function.

#### ETIOLOGY AND CHARACTER OF THE EXPERIMENTAL LESIONS

In speaking of the etiology of nephritis in man, excluding, of course, lesions due to the localization of bacteria, we use, owing to our inexact knowledge, the phrase "soluble toxic substances reaching the kidney through the circulation." So, in experimental nephritis a direct nephritic poison must be capable of absorption, of solution in the body fluids and of causing injury to the renal cells when given in doses so small as not to cause death through its other actions. An indirect poison acts through products formed by blood or tissue destruction, as with the hemolytic poisons, here the action on the kidney is secondary. If we exclude

Siegel's experiments on the production of nephritis by the application of cold, all forms of experimental nephritis are caused by substances falling in the above classification.

According to Sollmann, all metals, so far as they have been studied, cause nephritis, though some act only in corrosive doses or when given intravenously. Other nephrotoxic substances are alum, coal-tar products, alcohol, anesthetics, oxalates, cantharidin, essential oils, snake venom, ricin, abuin, bacterial toxins, hemolytic poisons and nephrotoxic immune serum.

Of these some act diffusely, while others affect the tubules or the glomeruli separately. Only such as have a more or less definitely circumscribed action are of value in producing experimental nephritis. Thus in the group affecting tubular epithelium with little or no primary glomerular injury, we may place, as most important, uranium nitrate, the chromates of potassium and of ammonium, and corrosive sublimate. Of those affecting glomeruli especially, the more important are arsenic, cantharidin and snake venom. All of these latter have some slight effect on tubular epithelium, probably secondary to circulatory disturbances dependent on the glomerular injury, but the latter lesion is so marked and so evidently primary that they are usually referred to as glomerular poisons. Another agent of value in experimental work is diphtheria toxin which combines glomerular and tubular injury.

All of these cause the appearance of albumin and casts in the urine, only uranium nitrate produces edema.

Although I have, thus far, used the terms "tubular" and "glomerular" in reference to these poisons they may more definitely be denominated, respectively, "epithelial" and "vascular" poisons. Until recently this division was made on anatomical grounds, that is, on histological evidence of degeneration, necrosis, exudation or cell proliferation but the study of nephritis by physiological methods has brought out evidence of the existence of functional glomerular injury of extreme grade accompanied by little if any anatomical evidence of vascular lesion. These methods have also shown that nephritides due to agents formerly supposed to act only as tubular poisons present, in the late stages of intoxication definite evidence of vascular incompetency.

It is necessary therefore to describe briefly the lesions produced by the more important nephritic poisons. This description will be limited to those poisons especially discussed in this address. It however by no means exhausts the list of substances which may be used.

The anatomical changes due to uranium and to the chromates, are, in the early stages confined essentially to the tubules especially the

convoluted tubules, and consist of granular or fatty degeneration and definite necrosis often affecting large groups of tubules. Corrosive sublimate causes similar lesions involving especially the ascending loops of Henle and characterized also by the deposition of lime salts. In these typical forms of tubular nephritis no anatomical lesions of the glomeruli are evident in the early stage, but in the late stages an ill-defined thickening<sup>1</sup> of the capillary walls may sometimes be seen and evidence of vascular disturbance is shown by physiological methods.

The glomerular form of nephritis varies. Arsenic, which acts through paralysis of the capillaries, causes little or no anatomical change in the glomeruli. The capillary loops may show slight thickening, the vessels may be overfilled, and the nuclei may stain peculiarly. Exudate into the glomerular space is usually absent, though a slight amount of coagulated serum may be present. By physiological methods, however, it is shown that despite the absence of anatomical lesions, serious vascular injury is present. Tubular involvement is slight and usually difficult to demonstrate.

Cantharidin causes a glomerular nephritis involving both the tuft and the capsular space. The lesions of the capsule have been variously described as desquamative, as consisting of a leucocytic exudate and as due to the presence of epithelial cells pushed up into the capsule from the convoluted tubule. Lyon has recently emphasized this latter view and also describes degenerative changes in the convoluted tubules and ascending loops of Henle with necrosis of the latter. Functional tests demonstrate serious vascular injury.

The venom of the rattlesnake, as I have recently determined, causes a very remarkable glomerulonephritis of the exudative type. Single large doses or repeated small doses cause an exudate of serum and fibrin in both the capsular space and the glomerular tuft. This exudate is usually but not always hemorrhagic. Leucocytes are not prominent, but occasionally are present. The tubular changes are slight or entirely absent.

Diphtheria toxin is the best example of those poisons which combine both epithelial and vascular injury. Hyaline thrombi are found in the glomerular capillaries and small arterioles of the cortex in acute and intense intoxication. The vessel walls show hyaline changes and, in the later stages, cyst-like hemorrhages in the tuft (Lyon). Leucocytes are abundant in the tuft and slight necrosis may occasionally be seen (Flexner). With these changes are found extensive degenerative and necrotic lesions of the convoluted tubules and the ascending loop of Henle.

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<sup>1</sup> In the uranium lesion, Christian has described hyaline droplets in the capillary loops.

Undoubtedly, the lesion in both tubular and glomerular nephritis occurs in that portion of the kidney through which the poison is eliminated, though this has not been definitely demonstrated except in the case of uranium.<sup>2</sup>

From this, and our knowledge of the elimination of iron through the convoluted tubules, it seems probable that nephritis, due to the salts of various metals, is an indication of injury at the point of elimination. The peculiar involvement of the loops of Henle in the corrosive sublimate lesions supports this view. It is not too much to hope that by careful study of such localized lesions, experimental nephritis may eventually contribute to our knowledge, not only of altered function, but also of the normal physiology of the kidney.

The glomerular lesions likewise must be considered as a special manifestation of a general injury to capillary structures, the intensification of that action in the glomerulus being due to concentration of the poison at the point of elimination.

At present, then, we are familiar with several poisons which affect either tubule or glomerulus, respectively, the injury being recognized sometimes by anatomical changes, sometimes by functional disturbances and sometimes by both.

The futility of judging of altered glomerular function by anatomical changes alone is best illustrated by Takayasu's histological study of the kidneys utilized by Schlayer and Hedinger in their investigations of disturbances of function in various forms of nephritis. This work will be discussed in detail later. Here it is sufficient to state that in arsenic and cantharidin nephritis characterized by constant and severe disturbance of vascular reactions, the glomeruli presented exudative lesions in only 2 per cent of the kidneys examined, and this anatomical condition reached a degree comparable to the functional disturbance only in those kidneys showing total insufficiency. Proliferative lesions of tuft or capsule were not demonstrable. The only frequent lesion was increase in size of the glomerular nuclei and an indistinct outlining of the capillary walls due apparently to an ill-defined thickening. The nuclear changes moreover, occurred in tubular as well as in glomerular nephritis. Such results would appear conclusively to establish the possibility of serious

<sup>2</sup> Schneider working with *Petromyzon fluvialis* injected uranium solution in the muscle of the back, and also subcutaneously, and found that by the use of a fixing fluid containing potassium ferrocyanide, picric acid and hydrochloric acid, the uranium was precipitated as a brownish-yellow deposit in the epithelium of the tubules.

functional disturbance with little or no evidence of structural lesion To this problem I shall return in the discussion of altered function

This brief description summarizes the more important types of acute injury caused by irritants acting directly on the kidney It remains to discuss the relation of these to the production of lesions which may be termed chronic nephritis, or are accompanied by manifestations characteristic of the chronic disease in man The production of such a condition has been the object of nearly all work on experimental nephritis, and until recently with no success Lyon, who worked with cantharidin, diphtheria toxin and corrosive sublimate, with the object of following acute lesions to their termination in chronic, found that acute lesions rapidly disappear and that the kidney returns to normal Such has been the experience of many other investigators, and has incidentally served to strengthen the clinical observation that an acute nephritis, if the causative agent be no longer active, may go on to cure without the development of subacute or chronic lesions This, however, is a phase of experimental nephritis which, in view of the very recent statement of Muller based on clinical observation and supported by the pathological studies of Lohlein, should again be investigated and especially with regard to the matter of glomerular lesions Muller expresses the opinion that a chronic nephritis may be the result of an acute lesion with a progressive course marked by acute exacerbations, or, on the other hand, there may be complete cessation of symptoms for many years with eventually a contracted or indurated kidney due to healing by scar formation

Lohlein, as the result of a very careful study of selected material, has shown that many individuals dying of chronic nephritis present a definite history of an acute nephritis, followed by a quiescent period of several years, before the appearance of the chronic lesion responsible for death His conclusions are based more especially on the kidneys of scarlet fever and acute coccus infections, in which he found inflammatory glomerular changes which seemed to be the starting-point of the fibrotic tufts and thickened glomerular capsules characteristic of the later developing chronic nephritis Such observations are not new Others have reported isolated instances of a chronic nephritis following the acute lesion of scarlet fever Thus Handford describes such a condition after scarlatinal nephritis in a child 12 years old, in whom the chronic condition developed three years after the acute, and Councilman describes a chronic interstitial nephritis with heart hypertrophy following scarlet fever, in a child of 2 years Similar findings have been reported by Leyden, Mann and others Lohlein's extensive and thorough study, however, brings the problem once more prominently before us, and, coupled with

the observation of Muller, makes it one of much importance. It would seem possible that by the use of a substance like venom, which acts as a definite glomerular poison and causes exudation and very striking endothelial destruction, experimental evidence of chronic nephritis following a single injury could be added to the clinical and pathological evidence now at hand.

Despite this possibility, it must be admitted that the experimental study of nephritis supports the more common conception of the etiology of chronic nephritis in man, that is, that it is a gradually developing lesion due to the long-continued insidious action of some ill-defined toxic substance. With the possible exception of the recent experiments of Dickson, the results obtained have been neither constant nor of such nature as to justify the term of chronic nephritis. Certainly if we take as a criterion, a persisting lesion of the kidney characterized during life by elimination of albumin and casts, and histologically by changes involving glomeruli, tubules and connective tissue, nearly all experimental efforts can be excluded. If we include edema as a necessary corollary, chronic nephritis has not been produced experimentally. Some of the methods which have resulted in lesions approaching chronic nephritis are, however, worthy of mention. Ophuls, who investigated this subject, came to the conclusion that the best results could be obtained with lead, and, by the prolonged administration of a lead salt, he produced in guinea-pigs and dogs a definite sclerosis. The urine, however, did not contain albumin and casts. The same objection holds for experiments with many of the other metals (Petoff).

The experiments of Ehlich and of Levaditi with vinylamin show that the primary necrosis of the papilla of the kidney caused by this substance may be followed by cortical injury with increase of connective tissue and considerable contraction. In a few of these experiments, in which mice were used edema, hypertrophy of the left ventricle and albuminuric retinitis were observed, with characteristic changes in the urine. Such changes, however, were not constant. The value of these experiments, moreover, is slight, for the diffuse nephritis followed destructive lesions of the papilla leading to mechanical obstruction, and were not due to a primary injury of cortical structures caused by a circulating poison, though it must be admitted that Lindemann has described the production of such injuries by the use of this substance.

Occasional positive results have been obtained with a variety of substances, as cantharidin (Aufrecht), oxalic acid and oxamid (Ebstein and Nicolaier), potassium chromate (Ophuls), and uranium nitrate (Siegel). I have myself found, in the course of a study which had for its object

the production of edema in the dog, a typical contracted granular kidney as the result of continued injections of potassium chromate and nephrotoxic immune serum. Chronic lesions, however, cannot be produced constantly by such methods and occasional positive findings, in view of the frequency of spontaneous lesions, must be regarded with suspicion. Or, to look at it in another way, these occasional positive results may have been due to the accidental presence of some secondary factor, as some metabolic or circulatory disturbance, necessary to the production of chronic nephritis. It was with this possibility in mind that Dr. Haven Emerson investigated experimentally the relation of circulatory disturbances to chronic nephritis. He recognized that, while a variety of causes are known to be responsible for, or contribute to, chronic interstitial changes in various tissues, there is almost constantly associated with them a circulatory disturbance usually a venous congestion. It might be objected that such a disturbance is the result and not the cause of productive lesions in man but Emerson's experiments are nevertheless of value, in that this hypothesis was, for the first time, investigated. The influence of vasodilatation and vasoconstrictors was tested by inhalation and by subcutaneous and intravenous injection. Inhalation experiments during a period of half a year caused the appearance of degenerative parenchymatous lesions with slight connective tissue changes. Though these experiments were few in number, the results, due apparently to disturbances of circulation and nutrition, suggest that with this background, the long-continued administration of a renal irritant in small doses might result in the fairly constant production of chronic nephritis. In this connection Cairo's observation that nephritis occurs in cats five to eight days after extirpation of the thyroid is suggestive.

In other words, the evidence at hand supports the theory that chronic nephritis should readily be produced as the result of an irritant action associated with, or causing, circulatory and nutritional disturbances. This is in accordance with our clinical and pathological knowledge of chronic nephritis in man.

In accord with this view, also, is Bradford's suggestion that the many failures to produce chronic nephritis are probably due to the fact that we have no irritant capable of causing in animals a condition analogous to acute nephritis with edema as seen in man. This statement was made in 1904. Such a substance we now possess in uranium nitrate, which, as Richter showed in 1905, causes a very definite acute tubular nephritis with the occurrence, when an excess of water is administered, of edema of the subcutaneous tissues and accumulations of fluid in the serous cavities of the body. Uranium nitrate has come into general use

as one of the most satisfactory of nephritic poisons, and Dickson, during the past year has shown that its prolonged administration causes chronic nephritis in a large percentage of the animals treated. Unfortunately, his choice of experimental animals did not allow a study of edema. If rabbits, in which edema is readily produced, had been used instead of guinea-pigs and the animals placed under conditions favorable to the production of edema it is possible that his results would have been the most satisfactory yet reported. As it is, he has shown (1) that prolonged administration of uranium nitrate causes a progressive "subchronic" nephritis, (2) that a series of six or seven acute attacks results in extensive fibrotic changes, with in some instances, granular atrophy and associated polyuria, (3) that single injections not infrequently cause more or less severe fibrosis with occasionally granular atrophy, and (4) fluid in small amounts was found in the serous cavities of a few animals.

These experiments are of great importance in connection with what has been said about the influence of circulatory disturbances in the production of chronic nephritis. Uranium nitrate, in addition to its very decided action on renal epithelium, also causes very definite vascular disturbances. Several investigators have been forced to this conclusion as Heineke and Meyerstein and Dickson. Recently, I have called attention to the necessity of assuming such an action in order to explain certain phases of the edema caused by this substance. Final proof of this vascular injury is furnished by Schlayer and his associates, who have shown, by physiological methods, that although uranium primarily affects the tubules there occurs a stage of glomerular injury characterized by dilatation of the vessels and decreased permeability. This will be discussed later in connection with edema, but these observations serve here to indicate the value of uranium in combining the toxic effects apparently necessary to the production of chronic nephritis by causing not only structural changes but circulatory disturbances also.

Thus may be summarized briefly the methods which have been employed in producing nephritis experimentally, the character of the acute lesions and the relation of these to chronic conditions. Such a statement is necessary as a preliminary to the discussion of functional disturbances.

#### FUNCTIONAL DISTURBANCE

The study of anatomical changes in experimental lesions adds little to our knowledge obtained by the investigation of human material. By applying physiological methods on the other hand we may correlate disturbance of function with any state of anatomical change and thus obtain information which clinical and pathological studies fail to give.

The kidney lends itself, perhaps more than any other organ, to investigation by physiological methods. The very abundant blood-supply with its intimate relation to the function of the kidney, the close relation of function to general blood-pressure and the influence of the circulation on diuresis, are conditions which readily allow the application of methods, the results of which may be graphically registered. Changes in kidney volume dependent on general blood-pressure or on the influence of its own independent vasomotor system may be measured by the oncometer, and the results for the normal compared with those in animals with experimental nephritis. Likewise a simultaneous study of diuresis allows of the determination of the changes in the elimination of fluid. The injection of various substances influencing blood-pressure or diuresis yields information concerning the reaction of the kidney to these stimuli, and by their use it is possible to differentiate between the disturbances due to a glomerular and to a tubular nephritis. Further information concerning disturbances of function due to tubular or to glomerular lesions, respectively, may be gained by the use of phloridzin, and by correlated studies of the protein and salt elimination. Some information, as the result of such investigations, especially in regard to diuresis, is offered by pharmacological studies, but the most comprehensive study of this kind has been made by clinicians, by Schlayer and his associates, and deals particularly with the vascular reactions in the two types of nephritis.

Their work is based on the assumption that the vascular reactions of glomerular nephritis should differ from those of tubular nephritis and that this difference should be readily determined by the action of certain stimuli, the effect of which would be to cause either contraction or dilatation of the vessels. These changes, through decrease or increase of the kidney volume, would be readily recognized with the aid of the oncometer. It was necessary to choose stimuli the effect of which would be but transient and which would cause no injurious after-results, thus allowing a series of observations on the same animal within a comparatively short space of time. Furthermore, as the conditions of experiment were such that observation on the same animal before and after the development of nephritis could be made only in short-period experiments, it was necessary to demonstrate that these stimuli exerted a constant effect on normal animals.

To test the capacity of the vessels to contract they used sensory stimulation (tobacco smoke in the nose or transient suffocation) as an example of effect through the vasomotor center, and adrenalin as an example of the effect of peripheral contraction. Each of these methods produced a transient diminution of kidney-volume with an increase at the same time in general blood-pressure. Caffein and strong salt solution were used for the purpose of producing dilatation of the renal vessels. In connection with all these conditions the relation of diuresis to vascular changes and the power of phloridzin to cause glycosuria were also studied.

In brief, the study was one of the reaction of the renal vessels to various stimuli and the relation on the one hand to general blood-pressure and on the other to diuresis.

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Necessarily, much depended on the uniformity of the control experiments for this reason rabbits of the same breed and similar weight were chosen. With the exception of adrenalin, all substances were injected in definite doses, and all but phloridzin, intravenously. Sensory stimulus (1 drop of 1 per cent solution in 0.5 cc normal salt solution) caused a fall in blood pressure with a corresponding fall in kidney-volume. In each instance this was transient, the normal condition being resumed in a very short time. On the other hand, 5 per cent salt solution (5 cc per kilo) and 10 per cent solution (2 cc per 1.5 kilo) cause a marked dilatation of the kidneys with strong pulsation and immediate diuresis, the general blood-pressure remaining unchanged. At the end of the experiment, phloridzin was given intravenously, this caused a moderate diuresis with glycosuria but without change in kidney volume or in general blood pressure.

These results were always obtained with normal animals. As the degree of reaction with each stimulus was practically the same in such observations as controls, a study was undertaken of various forms and differing stages of toxic nephritis. Potassium bichromate and corrosive sublimate were used for the production of tubular lesions, and arsenic, cantharidin and diphtheria toxin for vascular nephritis.

Schlauer's opinion concerning tubular nephritis is based on experiments with chromate and 15 with corrosive sublimate animals. Reactions to the various stimuli in the early stages of nephritis do not differ markedly from the normal. It was found that animals eliminated a larger amount of urine than do normal animals in accord with Weber's observations, and also that diuretics caused greater flow, as had also previously been demonstrated by Spiro. The vascular reactions differed from the normal in that the power of the vessels to contract after sensory stimulus was slightly increased and the power to dilate was greater to the same extent. Phloridzin acted as normally, that is, causing glycosuria.

The results with corrosive sublimate were similar except that polyuria before the administration of diuretics was not so marked. In both forms epithelial lesions were very prominent, but no changes were evident in the glomeruli. In short, the early stages of tubular nephritis with albuminuria and cast secretion are not accompanied by pathological changes in the tubular epithelium offer no physiological evidence of vascular injury.

Before taking up the late stages of tubular nephritis the vascular nephritis, for the sake of sharp contrast, may be mentioned. Cantharidin and arsenic nephritis offer the best examples. Severe vascular disturbances come on very quickly. In arsenic nephritis the early polyuria characteristic of the chronic disease disappears. Within four to eight hours the effect of sensory

adrenalin is much less than in the normal, and after the administration of diuretics the power of the vessels to dilate decreases and with it diuresis. As the nephritis proceeds to severer degree, or if larger doses of the irritant be given, the power to contract after sensory stimulus and adrenalin becomes minimal and dilatation and diuresis become slight or cease entirely. Under such circumstances phloridzin produces no diuresis and no glycosuria.

The lesions due to arsenic are similar to those of cantharidin except that the general blood-pressure falls more quickly and remains at a lower level. This is to be explained by a greater peripheral capillary injury or perhaps by more intense action on the vasomotor center.

This comparison is very instructive. A tubular nephritis with extensive epithelial destruction and a urine rich in albumin and casts give no physiological evidence of vascular disturbance except a slight polyuria and a slightly heightened response to vascular stimuli. On the other hand, in a glomerular nephritis with little or no evidence of anatomical injury to either tubules or glomeruli, and with comparatively slight albuminuria and cast excretion, we find that the capacity of the vessels to contract and dilate is greatly altered, and with this a corresponding inhibition of diuresis, which may go on to total insufficiency.

These observations demonstrate for the first time the possibility of primary injury to glomeruli and tubules, respectively, and offer a sound experimental basis for the conception of a vascular as contrasted with a tubular nephritis.

But how, ask those who object to the direct application of experimental evidence to the problem of human pathology, is this to help us in explaining the majority of renal lesions in man? We admit its value from a pharmacological point of view. We admit also the possibility of primary glomerular injury and primary epithelial injury, and also that occasionally the glomerular lesion, as in scailatinal nephritis, may remain the predominating lesion, and, on the other hand, that the acute renal lesions of certain intoxications, as cholera, eclampsia, and to a certain extent of diphtheria, may be purely epithelial lesions, but what is the bearing of this experimental evidence on those forms of nephritis in which both glomeruli and tubules are involved, and, most frequently, it would seem, the tubules first and more seriously? This question is a proper one, and while it cannot be fully met as yet, it is, I believe, answered in part by the studies which Schlayer and his associates have made of the later stages of tubular nephritis. They find that the late stages occupy a middle position between early tubular and typical vascular nephritis, and in severe forms may simulate the latter. The reaction

to sensory stimulus and adrenalin remains practically normal, but the power of dilatation and diuresis, after the administration of diuretics, decreases gradually, and in severe late stages, that is after two to four days, dilatation is very slight or absent and diuresis does not occur. Phloridzin no longer causes glycosuria. These changes may be accompanied by slight histological alterations in the glomeruli, but the condition is, essentially, a functional glomerular disturbance following tubular injury. That this secondary glomerular involvement is a true vascular disturbance and not the result of compression of the glomeruli, due to the retention of urine in tubules blocked by casts, Schlayer and Hedinger have shown by experiments in which the ureters were ligated. Under such conditions no vascular disturbance resulted. Thus these investigators have demonstrated not only tubular and vascular nephritis as experimental conditions but have shown that the former may develop into the latter. The relation, however, of the late glomerular changes to the early epithelial changes cannot be explained without more complete experimental evidence. That the late vascular injury is due to the original poison is doubtful but the possibility must be considered, in view of the fact that in Schlayer's experiments with diphtheria toxin, a gradually developing nephritis of the tubular type passed, after only twenty hours, into the typical vascular type. Again, it is possible that the tubular nephritis may cause the development of secondary poisons, consequent on metabolic disturbances in other organs, and capable of affecting the glomeruli. In this connection must also be considered the matter of the "give and take" of renal function recently emphasized by McCrae. This theory assumes the possibility of the glomeruli taking over in part at least the function of the tubules. It is possible that substances normally passing through the tubular epithelium are, when the latter is destroyed, eliminated by the glomeruli the endothelial cells of which may be more susceptible to injury by such substances than is the tubular epithelium.

These are some of the problems suggested by Schlayer's work, which await the verdict of further experimentation by physiological methods. During the past year I have been interested in certain phases of these problems and have repeated Schlayer's experiments, using the dog rather than the rabbit, because of the more stable circulatory mechanism of the former. The vascular reactions of the two types of nephritis, observed in the rabbit, I have found to occur also in the dog. The tubular form likewise develops into the atypical vascular form.

<sup>3</sup> Pearce R. M., Hill M. C., and Eisenbrey A. B. Experimental Acute Nephritis. The Vascular Reactions and the Elimination of Nitrogen. *Jour. Exper. Med.* 1910, Vol. No. 2.

Additional evidence of the distinction between tubular and vascular nephritis is offered by chemical studies which, with the assistance of Dr. Miner C. Hill, were carried out in connection with the experiments just mentioned.<sup>3</sup> These depend on our knowledge that most, if not all, of the urinary nitrogen is eliminated through the tubules, and on the assumption that in tubular nephritis this elimination would be diminished. Daily estimations of the total nitrogen elimination in animals with tubular and glomerular nephritis, due to uranium nitrate and arsenic, respectively, were made. It was found that in the tubular nephritis a decrease of nitrogen equal to 9 to 14 per cent of the normal elimination occurs, while in the glomerular form this decrease does not occur. Indeed the arsenic animals showed an increased elimination varying from 7 to 16 per cent, demonstrating that the tubules not only were not injured, but also that they were able to care for the augmented output of nitrogen consequent on the increased metabolism due to arsenic.

These observations are of twofold interest. In the first place, the work with arsenic offers additional evidence of the possibility of producing a glomerular disturbance without affecting the function of the tubules, and, on the other hand, the diminished excretion of nitrogen in tubular nephritis<sup>4</sup> indicate the possibility of a retention leading to a disturbance, not only of the glomerulus in the "give and take" of kidney function, but responsible perhaps for some of the more general manifestations of nephritis.

Here may be introduced also other evidence, of an entirely novel nature, which is of value in the differentiation of tubular and glomerular nephritis, and which would appear to be of definite physiological importance in the matter of normal tubule function. I refer to my recent investigations of the depressor substance of dog's urine, and I do this with some hesitation, as the application of the observation to the nephritis of man is not at all clear.

Elsewhere, in a discussion of the influence of kidney extracts on the blood-pressure, I have described the very striking depressor influence of dog's urine, when injected intravenously into other dogs. At that time this observation was of interest only in that it appeared to indicate that the similar depressor influence exerted by extracts of the dog's kidney was due to the content of urine which could not be removed.

My interest in this peculiar manifestation was again aroused by a chance observation made during the course of a recent study of diuresis.

<sup>4</sup> Siegel also describes this decreased elimination of nitrogen in uranium nephritis, and Green, in a recent study of chromate nephritis, found a decrease of 20 per cent.

in the pathological kidney Dog's urine, on account of its very decided depressor influence, from which the animal quickly recovers, was used in this work as a means of rapidly lowering the blood-pressure

It served most satisfactorily for this purpose and never failed with a large series of normal urines Early in the investigation, however, it was observed that the urine from an animal in the third day of a chromate nephritis failed to cause the usual depressor effect This chance observation led to the routine investigation of the urine of animals with various forms of experimental nephritis As a result it was found that the depressor substance disappeared about the third to the fifth day from the urine of those animals suffering from renal lesions characterized by extensive tubular injury and persisted after the administration of substances causing glomerular injury with little or no tubular change<sup>5</sup>

This difference suggests that in the tubular lesion of chromate and uranium nephritis which is characterized by extensive epithelial destruction, some substance normally eliminated is retained, while in the glomerular nephritis, caused by arsenic and cantharidin, this retention does not occur The elimination of the depressor substance would appear, therefore, to be a function of the tubular epithelium This view is supported by a study of the effect produced by normal urine as compared with that passed at the height of diuresis Thus, in one animal the urine obtained from the bladder at the time of inserting the cannula, caused a drop of pressure of 64 mm Hg, whereas at the height of caffeine diuresis, the drop was but 30 mm In another animal the figures were 60, 32 and 16 for (1) the normal urine, (2) the beginning and (3) the height of diuresis, respectively This indicates that the increased glomerular filtrate either dilutes the depressor substance eliminated by the tubule, or it passes through the tubules so rapidly that this substance is not added in the usual amount

In animals with experimental nephritis of the tubular type the disappearance of the depressor substance<sup>6</sup> from the urine is frequently asso-

<sup>5</sup> Pearce R. M. Concerning the Depressor Substance of Dog's Urine and its Disappearance in Certain Forms of Experimental Acute Nephritis *Jour Exper Med.*, 1910, **xii**, No 2

<sup>6</sup> Concerning the exact nature of this depressor substance I have no knowledge It dialyzes slowly is not destroyed by boiling for a few minutes but does disappear after prolonged heating It can, however, be completely precipitated from the urine in impure form by large amounts of alcohol The precipitate thus obtained, when dried and brought back to original volume with distilled water, has a depressor effect equal to that of the untreated urine, while the filtrate evaporated at room temperature to original volume has no effect whatever The precipitate is not a single substance, but contains phosphates, chlorids and sulphates and has a very small nitrogen content

ciated with a lowering of the blood-pressure, which would appear to indicate that the retained depressor substance may have a definite effect on the general blood-pressure. This observation is not, however, based on blood-pressure determinations on the same animal, before and after the development of nephritis, but by contrasting the pressure in animals with tubular nephritis with that in normal animals. It may, as is true in glomerular nephritis, be due to some other factor affecting the vascular system generally.

Investigations now in progress will, I hope, throw more light on the nature of this depressor substance, and, I trust, on the significance of its disappearance from the urine. At present the latter is of importance, as a manifestation of tubular nephritis, as contrasted with glomerular nephritis, as an indication of possible normal tubule function, and possibly, also, as an explanation of certain conditions of low arterial tension in man. Concerning the latter we have little information, for clinical studies have been confined largely to the condition of hypertension. It is of interest, however, that in the disturbances following too great experimental reduction of the dog's kidney, a condition of acute renal insufficiency, Janeway has demonstrated a definite fall in general pressure. If it could be shown also that the depressor substance disappears from the urine of these animals we would have a very substantial basis for a theory of acute renal insufficiency of tubular origin leading to hypotension.

It is perhaps needless to say that such observations have apparently no bearing on the hypertension of scarlatinal nephritis or that of the interstitial type of chronic nephritis. Also, one cannot assume that the experimental conditions here described hold for human nephritis. At present they must be considered merely as interesting experimental observations concerning the influence of the kidney on blood-pressure, and although it brings to this subject some confusion and uncertainty, future investigations may add unexpected knowledge, perhaps, in the direction of a better understanding of tubule functions.

#### EDEMA

As edema is, in many ways, the most striking manifestation of certain forms of nephritis in man, it is natural that it should be considered in a discussion of experimental nephritis. I will not attempt, however, in this connection to present the conflicting views concerning the physiology of lymph formation or the general pathology of edema, which are admirably set forth in Meltzer's lectures on this subject, but will limit myself to the recent studies due to the stimulus of Richter's demonstration that acute uranium nephritis in animals is accompanied by edema.

The older literature contains much experimental evidence concerning the importance of hydremic plethora or of vascular injury (Cohnheim and Lichtheim, Magnus, Albu) in the production of renal edema, but as this is for the most part based on transfusion experiments in which large amounts of fluid were used, or experiments on dead or nephrectomized animals, it is not entirely satisfactory, as the conditions are too artificial. The results of such experiments are based on the absence of kidney function rather than on the influence of the altered function of the diseased kidney. Only uranium nephritis, of the various forms of experimental renal disease, is accompanied by a spontaneous edema, and thus offers experimental conditions analogous to nephritis in man.

The more important theories of renal edema may be briefly stated. On the one hand are those who support the importance of hydremic plethora as enunciated by Grainger Stewart and Baetels, but more or less modified by later investigations, as those of Roth-Schultz and others. On the other hand, are those who consider hydremic plethora of secondary importance, and, following Cohnheim, ascribe to the injury of peripheral capillary blood-vessels, the important rôle. With this theory is closely associated that of Senator, who presupposes injury of the renal vessels as well as of the peripheral vessels.

There is a tendency to bring these explanations together, giving each its share in a theory which ascribes the cause of edema to the combined influence of renal vessel injury and peripheral (cutaneous) vessel injury, the former leading to retention of water or salts, or both, and the latter responsible for the increased permeability of the capillaries at the site of the local accumulation of fluid. In brief, the problem has become essentially that of the relative importance of vascular injury, hydremia and salt retention. Since the demonstration of the value of uranium nitrate<sup>7</sup> for the production of a nephritis with edema, the influence of these factors has been extensively reinvestigated.

7 It is a matter of local interest that, although macroscopic evidence of renal injury due to uranium was observed by Leconte in 1854, the first carefully recorded observations on uranium nephritis were from Professor Chittenden's laboratory at New Haven, and in 1889, in a communication from this laboratory, Professor Chittenden and Dr Alexander Lambert of this city first described ascites in connection with uranium poisoning. Woroschilsky in the following year, in a communication from the pharmacological institute at Dorpat described, accurately, diffuse edema of the skin and subcutaneous tissues and the accumulation of fluid in the serous cavities of the body. These observations were, however, either overlooked, or their importance not appreciated, for it was not until 1905, when Richter's communication appeared, that the importance of this experimental lesion was generally recognized.

Richter found that rabbits receiving subcutaneously small doses of uranium nitrate and at the same time 100 c.c. of water daily by stomach-tube, developed a well-marked edema of the subcutaneous tissue with the accumulation of considerable amounts of fluid in the serous cavities. This edema, it is true, differs in two respects from that of nephritis in man.

1. There is a greater tendency for the fluid to accumulate in the serous cavities and subcutaneous tissues than in the skin proper. This is probably due to histological differences between the skin of man and the rabbit but is not of great importance, for the widespread edema involving the subcutaneous tissues of the abdomen and thorax and frequently extending to the neck, head and extremities, is sufficient evidence of general edema.

2. The fluid is richer in albumin and tends to clot more readily than is the case in man. There is, however, no evidence that this fluid is of inflammatory origin, the high albumin content is probably to be explained by the acute character of the lesion, and in this regard approaches the character of the fluid in the edema of scarlatinal nephritis.

Despite these slight differences the picture is sufficiently similar to the edema of man to be considered a true experimental nephritic edema, and is so regarded by the large number of investigators who have confirmed Richter's observation.

The studies of uranium edema fall into two groups those bearing on the question of water and salt retention, and those dealing with vascular injury. The first group includes experiments in which artificial plethoric hydremia is produced and those in which the salt content of the body fluids is increased by administration of sodium chloride. The second group includes physiological studies of the renal vessels in uranium nephritis and also the study of the influence of vascular poisons in those forms of experimental nephritis not ordinarily accompanied by edema.

The literature of water and salt retention in nephritis, which is voluminous and most confusing and contradictory, need not be summarized. The matters of greatest strife are (1) whether salt retention or water retention is primary, (2) if the salt retention is primary, whether it is a true tissue retention or secondary to vascular lesions which render the glomeruli less permeable to the salt. In either case the water retention is considered to occur as a result of the salt retention. The third possibility is that both water and salt are retained simultaneously as the result of glomerular injury.

The experimental evidence, based on altered kidney function in animals, which was at hand previous to the study of uranium edema, may be illustrated by two types of experiment. Beck and Glucinski, as well as Lepine, had demonstrated that temporary ligation of the ureter of one kidney was followed by a lessened

elimination of chlorids as compared with the opposite sound kidney, thus favoring apparently the theory of decreased renal permeability. On the other hand, Castaigne showed that, although there is a diminished chlorid excretion in dogs with experimental nephritis, as compared with normal dogs, this difference was not observed if the respective animals received salt solution in the renal artery. In other words, if the salt was brought to the kidney, the kidney could excrete it. In other experiments normal and nephritic animals were bled and the blood replaced by saline solution. Shortly afterward 200 cc of blood taken from the renal artery of each showed the salt content to be less in the animal with nephritis. These experiments are usually quoted as evidence of primary retention of chlorids in the tissues. It must be borne in mind, however, that in these experiments the renal lesion was not one accompanied by a spontaneous edema.

In the early work on uranium edema it was found that the administration of water in excess was essential for the development of a frank edema, though occasionally, as in Georgopoulos's series, a slight or moderate grade of edema occurs in unwatered animals.

Richter took up the question of the relation of hydremia to salt retention. He has found that if both salt and water are administered to animals a greater edema is produced than with water alone. On the other hand, salt without water has no power to increase the hydrops, and if salt is given with half the amount of water usually administered, the edema is not appreciably greater than in those receiving water only. On these observations and the demonstration that chlorid retention occurs in other forms of experimental nephritis without the occurrence of edema, Richter concludes that water retention is more important than salt retention.

Georgopoulos has utilized uranium nephritis to determine the matter of chlorid retention by direct quantitative analysis of the body fluids and tissues. His conclusions are very definitely stated as follows:

In uranium, as well as in cantharidin nephritis, no constant relation exists between the water and salt excretion; more water than salt is retained, thus leading to a decrease in the chlorid content of the blood. This indicates that water retention is dependent on a primary disturbance of the water-eliminating power of the kidney and is not secondary to chlorid retention. Moreover, an increase of chlorids in the tissues with a reduction of chlorid concentration of the blood could not be demonstrated in animals, with or without edema.

Schirokauer, in a similar investigation, found that in edema, although the tissues had a salt content greater than normal, it was no greater than the salt increase in the blood and in the hydropic fluid of the body cavities. The increased salt content of the tissue does not therefore support the theory of primary salt retention, but indicates rather that in the process of transudation the salts and water leave the vessel in the same percentage relation, one to the other, as they occur in the blood. Other important studies are those of Bence concerning the altered distribution of water in the body and of Heineke

and Meyerstein dealing with salt and water relations. The results of the latter, in that they indicate that salt retention may precede water retention, are not in accord with the other investigations quoted, but I have I believe sufficiently illustrated the value of uranium nephritis in the study of this phase of experimental edema and also shown that the bulk of evidence does not support the theory of primary salt retention.

Of even greater interest are the recent experimental observations concerning the importance of vascular injury. It was early recognized that although the administration of water in excess was necessary for the development of uranium edema, this was not the essential factor, for the administration of water with or without salt to animals with chromium, algin, cantharidin and other forms of nephritis did not cause edema despite the fact that in some of these forms, as chromium nephritis, the histological changes are practically the same as those of the uranium disease. Such observations naturally recalled the early experiments of Cohnheim and Lichtheim concerning the importance of vascular injury, due to various forms of irritation of the skin, and those of Magnus, in which vascular poisons, as arsenic, chloroform and ether were used, and suggested the possibility of an action of uranium, or of substances formed during the course of nephritis, on the blood vessels, both renal and peripheral. Several investigators (Blanck, Heineke and Meyerstein, Georgopoulos and Pearce) have expressed opinions to this effect. It remained however, for Schlayer and his associates, Hedinger and Takayasu, to demonstrate by physiological methods a functional disturbance of the renal vessels in uranium nephritis, which disturbance, apparently is an important factor in the production of edema. Uranium nephritis, it may be again emphasized, is anatomically of the type of tubular nephritis and characterized by extensive destruction, even to necrosis of complete tubules, and by abundant elimination of albumin and casts. Anatomical changes in the glomeruli, aside from slight thickening of the capillaries, the outlines of which are more or less indistinct, are not evident. Schlayer attacked uranium nephritis by the same methods which had served to differentiate tubular and vascular nephritis. It was found that in the early stages as well as in the late stages, uranium gives the reactions of a true tubular nephritis, of the type of the chromate or the corrosive sublimate disease. It has, however, an intermediate stage which differs strikingly from both the pure tubular and the pure vascular forms and which Schlayer has observed in no other form of nephritis except once in that form due to diphtheria. I may repeat, in order to present this peculiar reaction more clearly, that the characteristic feature of vascular nephritis is the failure of dilatation

of the vessels with little or no diuresis after the administration of diuretics. These manifestations also occur in the late stages of tubular nephritis. They occur also at the end in uranium nephritis, but preceding it is an intermediate stage, during which the administration of 5 per cent sodium chlorid causes extreme dilatation with strong pulsation but no corresponding diuresis. This stage develops thirty-six to forty-eight hours after the onset of the experimental disease at a time when no edema is evident, but when the urine is decreased in amount as compared with the preliminary polyuria. The vessels react to contraction stimuli strongly, the blood-pressure shows no change, the power of dilatation of the vessels is maintained but is unaccompanied by flow of urine. This occurrence, which was observed in fourteen animals, would appear to be definite evidence of decreased permeability of the glomerular vessels, marking a pre-edemic stage, during which a retention of water and salt occurs. Later, when the renal dilatation fails, the capillaries of the general circulation presumably become permeable and edema develops.

This phenomenon has one peculiar phase. Some minutes after the inhibition of diuresis caused by the salt injection a few drops of urine are excreted, but no further improvement in the flow of urine occurs. If, after a lapse of twenty minutes or so, caffeine is injected, the kidney volume, which has fallen, increases to the maximum attained after the previous salt injection, and a slight or moderate diuresis occurs. This diuresis is not so great as normal caffeine diuresis but is more prolonged, and the kidney-volume does not return to its normal level. That the production of diuresis under these circumstances is peculiar to caffeine was shown by the fact that if the injections were reversed, caffeine given first and followed by salt, each produced the same effect as before. Also it was impossible to cause diuresis by the administration of other diuretic substances, as urea, dextrose and sodium sulphate, though all cause dilatation of the blood-vessels.

That caffeine alone produces diuresis in this stage is of interest pharmacologically, as Schlayer has pointed out, in that it supports those observations which ascribe its activity to a purely secretory process. Also from a therapeutic point of view it is well known that the action of caffeine in nephritis in man may differ from that of the saline diuretics.

Several objections might be raised to the view that the essential lesion in edema is a diminished glomerular permeability. All of these, however, are met by Schlayer's carefully controlled experiments. It might be objected that the strong sodium chlorid solution itself produces the glomerular injury. That salt is harmful to the normal kidney has been frequently demonstrated, and Castaigne and Rathery have shown that the injection of normal salt solution into rabbits with injured kidneys causes an increase in albumin elimination. Against this objection we have the observation of Schlayer that urea and dextrose, certainly non-toxic in the doses used, had the same effect.

strong salt solution Other objections, as that based on the theory of primary salt retention and the assumption that the body had almost reached its limit of salt fixation at the beginning of the experiment, and that the half-gram of salt injected was sufficient to bind the water so that no diuresis could occur, are met by experiments in which three-hundredths of a gram of salt produced about the same decrease in diuresis as did the half-gram, which should not be the case if these objections were valid The objection that a salt retention associated with an early increased permeability of the peripheral vessels might account for the edema is met by experiments which show that no edema could be produced, during this intermediate stage, by transfusing the tissues with salt solution, whereas it could readily be produced in the final stage In brief, the control experiments indicate that the increased permeability of the peripheral vessels follows, and is presumably the result of the glomerular impermeability

One must admit the importance of Schlayer's observation concerning this peculiar condition of the renal vascular system in the intermediate stage of uranium nephritis, a functional disturbance which occurs only in that form of experimental nephritis which leads to edema It is the strong point of a theory of edema which reconciles many of the conflicting views on this subject Decreased glomerular permeability, occurring primarily and causing a retention of water and salts with secondarily an increased permeability of the peripheral blood-vessels is a convincing theory, and perhaps more than a theory, when the experimental work on which it is based is considered Certainly the experimental evidence which Schlayer offers shows that, if either of these factors is absent, no edema occurs

Concerning the importance of these factors, I have reached similar conclusions as the result of a study somewhat different in nature Accepting Schlayer's opinion that a vascular lesion is essential to the production of edema I have attempted to produce edema in true tubular nephritis by the administration of vascular poisons The relative importance of hydremia and vascular and renal injury was also studied Potassium chromate was used to produce a type of experimental nephritis almost exclusively tubular and not accompanied by edema For the production of vascular injury, rattlesnake venom, ricin and arsenic, all well-known vascular poisons, were utilized Water administered by stomach-tube in amounts of 100 c.c. daily, brought about a condition of plethoric hydremia A large number of rabbits were used, some received all three of these substances, some only one, and others various combinations of two, thus all possibilities were controlled

It was found that edema resulted only when the three factors of renal injury, vascular injury and hydremia were present. No one of these factors acting alone and no combination of two was sufficient to cause edema. The experiments in which venom was used were particularly valuable in that evidence of injury of the renal vessels as well as of the peripheral vessels, was offered by easily demonstrable hemorrhagic lesions of these structures.

From this summary it is readily seen that the study of experimental nephritis has added much to our knowledge of the relative importance of glomerular injury, hydremia, salt retention and peripheral vessel injury in the production of edema. This knowledge has been obtained in the only way possible, that is, by the study of a form of experimental nephritis accompanied by spontaneous edema.

#### TOXIC SUBSTANCES IN EDEMA

In connection with the phases of experimental nephritis just discussed, the next problem is the determination, if possible, of the character or nature of the substance or substances concerned in the production of the vascular lesions, both renal and peripheral, but especially the latter, in nephritic edema. Clinical and pathological studies offer no assistance. The early appearance of the prominent glomerular lesion of scarlet fever naturally suggests that the products of the etiological agent of scarlet fever are responsible for this lesion and possibly also, as Senator has suggested, for the vascular lesions of the associated edema of the skin, but in the absence of definite knowledge of the etiology of scarlet fever or of its toxic products, no conclusions can be drawn. Likewise in certain infections, as with the pneumococcus and streptococcus (Councilman), in which capsular and intracapillary glomerular lesions are sometimes seen, the toxic products of the infecting organism may be considered responsible for the renal lesion. On the other hand, in those forms of chronic nephritis in which edema most frequently occurs, the etiology is obscure, the relation of parenchymatous to vascular lesions uncertain, and therefore conclusions are impossible. Even though it be granted that the general vascular lesions of the acute forms of glomerular nephritis are due to the poisons of the primary disease, our lack of knowledge of the toxic factors in chronic nephritis leaves no explanation for peripheral vascular lesions. The study of experimental lesions of the kidney has thrown little light on this problem, but certain observations with the serum of animals with experimental nephritis are very suggestive of the mode of development of peripheral vessel injury. Thus Heineke found that rabbits with chromate nephritis, which is not characterized by

edema, developed edema when injected with the serum of animals with uranium nephritis. This phenomenon, since confirmed by Blanck, who, however, finds that it is not a constant occurrence, suggests that in the serum of animals with nephritis substances occur which operate to produce edema. Two explanations seem possible either the retention, as the result of kidney insufficiency, of substances which act as lymphagogues of the second order, or the injurious action on the endothelium, of some substance or substances causing an alteration in its permeability to fluids. The latter of these explanations is naturally more in accord with the experiments of Schlager and his associates and with those which I have described. In a later series of experiments with Meyerstein, Heineke supports the theory of injurious action on blood-vessels. In this study is reported the production of edema in 64 per cent of chromate animals receiving uranium serum intravenously, but edema was also found in an equal number receiving normal rabbit serum. As chromate nephritis, in the absence of serum injection does not cause edema, it is suggested that the serum in both instances had some injurious effect on the blood-vessels. Of similar import are the results obtained by Georgopoulos, who produced a moderate edema by injecting nephrectomized rabbits with the serum of animals suffering with uranium nephritis. In some of my own experiments with chromate nephritis I have found it possible to produce in the rabbit moderate grades of edema by injecting an alien serum (dog), and an edema equal to that of uranium nephritis, by using nephrotoxic immune serum (dog).

Despite the difficulty of explaining Heineke's results with normal serum, the various observations presented suggest very strongly the presence in the serum of nephritis, of elements acting on vascular endothelium. Whether such substances are the retained products of metabolism or whether they are substances formed anew, in the course of nephritis, or are possibly due to disturbances in those organs characterized by internal secretion, it is impossible to say.

Such observations must fall in the same category as those of Lindemann, Bierry, Sawyer and myself, concerning the power which the serum of various forms of nephritis (chromate, uranium, spontaneous, and that due to nephrotoxic immune serum) has when injected intravenously, of causing albuminuria and cast excretion in normal animals. The effect of the serum in each group of observations suggests the influence of the common factor, the renal disturbance, but unfortunately, while suggestive, the observations are as yet of so indefinite a character that they cannot be applied to human renal pathology. They would appear, however, to form a promising basis for future experimental investigation.

## THE STUDY OF CHRONIC RENAL INSUFFICIENCY

In this presentation I have thus far limited my discussion to those problems to which have been applied methods which offer a functional conception of the acute disturbances in nephritis. For this reason I have considered only those lesions to which may be applied the term "nephritis" without fear of contradiction. Such lesions are, for the most part, those of acute nephritis, and thus the problems of chronic nephritis, as uremia, hypertension, and heart hypertrophy, have necessarily been excluded. The experimental investigation of these latter phases of nephritis, because of the inability to produce constantly chronic lesions, has been attempted by means of the so-called reduction experiments in which, by operation, the kidney substance has been reduced to a minimum compatible with life. Such experiments have yielded information of much interest, and, although strictly speaking, they represent the effect of insufficient function, rather than the effect of a true nephritis, they may, I think, be discussed here in connection with the general problems of renal pathology.

## DISTURBANCES OF METABOLISM AND UREMIA

By the study of the metabolism in animals with experimental nephritis one might expect to obtain information concerning disturbances of elimination, or of the influence of the kidney lesion on general metabolism, and thus throw some light on the conditions determining the development of uremia. Such studies do offer some information of early or mild disturbances manifested by diminished nitrogen elimination (Siegel, Green) but in the severer lesions, the early occurrence of vomiting and diarrhea with inability to ingest, retain or utilize properly the food administered, all symptoms evidently of renal insufficiency, so disturb the nitrogen equilibrium that metabolism studies are impossible. This is true, not only of experimental nephritis, but also of those procedures by which the renal substance is greatly reduced by successive extirpations. Such experiments have therefore added but little to our knowledge of disturbances of metabolism as obtained by clinical studies. The reduction experiments bear particularly on the influence of the kidney on general metabolism. In the first important investigation of this subject, that of Bradford, the conclusion was reached that slight reduction was followed by an increase in the elimination of water, but no change in the solids, on the other hand, an increase in total solids was found to occur after the removal of three-fourths of the total kidney substance, an absolute increase when food was taken and a relative increase when the gastrointestinal disturbances were present. As the blood and tissues under the latter circumstances showed an increase in nitrogenous extractives, Brad-

ford concluded that these disturbances were due, not to retention of products of normal metabolism, but to an increased tissue catabolism, affecting especially the muscles.

Recently Bainbridge and Beddaid have repeated these experiments. They find that the increase of nitrogen elimination is not constant and occurs only during the last few days of life when the animals show a loss of 22 per cent of body weight, the result of gastrointestinal disturbances and loss of appetite. They conclude, therefore, that the kidney has no influence on nitrogenous metabolism, and that the disturbance of nitrogen elimination is to be ascribed to inanition, and is similar to that occurring in fasting animals. My own experiments on this subject led to conclusions in entire accord with those of Bainbridge and Beddaid. It would therefore appear very probable that mere reduction of kidney substance, even to a minimum compatible with life, does not lead to disturbances of metabolic function capable of being utilized in the explanation of uremia. Likewise these experiments indicate the improbability of the presence of an internal secretion of the kidney capable of influencing general metabolism.

It is evident, however, that although under such circumstances there is no disturbance of general metabolism which may be recognized by chemical examination of the urine, the very striking gastro-intestinal disturbances must be explained through some fault of kidney function. As these disturbances occur also in experimental nephritis of the tubular type (uranium, chromium and corrosive sublimate) and not at all or to but a slight extent in the vascular form (arsenic), they would appear to be due to a fault of tubule function, and the natural inference is that these disturbances are to be explained by a vicarious elimination into the gastro-intestinal canal of toxic products normally eliminated by the kidneys, and presumably are the manifestations of experimental uremia.

Some support of such a theory is offered by clinical studies of uremia by Von Noorden and his associates, who have found such a vicarious elimination, with an increase of ammonia nitrogen, to occur especially in the so-called uremic diarrhea.

In one of my early investigations I tested this theory as far as fecal nitrogen is concerned in animals with kidney reduction, but with negative results. More recently, with the assistance of Dr. Hill, I have estimated the total nitrogen elimination in urine and feces in a group of animals with various forms of experimental nephritis. A constant decrease in urinary nitrogen varying from 9 to 14 per cent was noted in the tubular form of nephritis, during the few days preceding the development of gastro-intestinal disturbance, but at no time was the fecal

nitrogen appreciably altered Siegel in similar experiments has also found the same drop in urinary nitrogen without an increase in fecal nitrogen

Metabolism studies, therefore, indicate that the alimentary disturbances are not due to vicarious elimination of nitrogenous substances into the intestine, or, on the other hand, to diminished absorption of such bodies therefrom. It may be possible, as I have suggested elsewhere, that toxic substances, non-nitrogenous in nature, which cause irritation by elimination into the intestines, are responsible for this disturbance; or that, accumulating in the blood, they act either through the central nervous system, or locally on the tissues with which they come in contact.

This problem I consider one of the most important offered for solution by experimental nephritis. The gastro-intestinal disturbances with the associated respiratory and circulatory disturbances, and, not infrequently, a period of unconsciousness, essentially coma, for several hours before death, constitutes a syndrome characteristic of renal insufficiency, and presumably, of experimental uremia. It is not too much to assume that the determination of the factors responsible for this experimental condition may explain some phases of uremia in man.

#### HYPERTENSION AND HEART HYPERPLASIA

the kidney substance, approximately two-thirds to three-fourths, by successive operations, a rise of blood-pressure occurred which was permanent and associated with cardiac hypertrophy and the elimination of an increased amount of urine of lowered specific gravity. This result was not constant, but occurred in about 25 per cent of the animals which survived, by at least four weeks, a considerable reduction of the kidney substance. In such it was observed also that arterial spasm with further rise of blood-pressure quickly followed stimuli which in normal animals would produce little effect. These observations suggest that the heart hypertrophy is due to increased work resulting from the circulatory disturbances caused by the tendency to arterial spasm, and that the vascular spasm is due in its turn to the effect of retained toxic substances.

The determination of the blood-pressure in these experiments was by direct measurement in the femoral artery, single readings were made before operation and one or more after operation. Although the differences noted, varying from 15 to 29 mm Hg with an average of 21.5, are quite definite, they are open to objection, as Theodore C Janeway has pointed out, on account of the well-known normal variations in pressure which occur from time to time. To obtain more definite information of the changes from day to day, Janeway has utilized in such experiments the universally accepted clinical method of determining blood-pressure. He has modified the Riva-Rocci cuff so that it may be applied to the foreleg of the dog, and the pressure determined with a minimum of error, estimated at about 10 to 15 mm. This method of measurement he has used on animals in which the renal substance had been reduced by Carrel's method of ligating several of the branches of the renal artery. Observations on such animals, in some instances covering a period of fifteen months, show, as compared with the normal readings before operation, a decided increase in pressure, thus in one animal was observed an increase from the average normal pressure of 90 mm to an average of 125 mm after 100 days, in another an increase from 117 to 150 mm. The maximum and minimum pressures of the respective daily observations showed also the same relative increase.

From a consideration of the experiments of Passler and Heineke and of Janeway, one cannot but conclude that a condition of experimental hypertension of renal origin is brought about as a result of the reduction of kidney substance. Such experiments, however, as yet offer no explanation of the mechanism by which the hypertension arises. It can hardly be due, in the extirpation experiments, to the influence on function of mere reduction of kidney tissue, for as I have shown, the "factor of safety" for the kidney is such that one-half of one kidney appears to be

sufficient for the proper elimination of nitrogen and presumably also for other solids. Nor in the ligation experiments of Carrel and Janeway can it be due to the mechanical effects of the reduction of the kidney circulation, for, as Ludwig has shown, complete ligation of the renal arteries is not followed by permanent increase in the general blood-pressure. The single anatomical condition which is unavoidable and follows all forms of injury is a varying degree of infarction-necrosis. This is slight in amount in the "polar" excisions of Sampson and myself, somewhat greater in the "wedge" excision of other investigators, and from the nature of the injury must reach its maximum in the ligation experiments of Carrel and Janeway. In itself this infarction cannot be responsible for hypertension, but the persistent albuminuria in Janeway's dogs indicates that it may be responsible for the development of a true nephritis which, of course, adds to the factor of diminution of functional area that of altered function. Similarly in the extirpation experiments, the irritation of sutures in the pelvis of the kidney, causes occasionally the localization of the colon bacillus with infection of the infarcted tissue and the development of a pyelonephritis (Sampson and Pearce), which must exert an injurious action on the remaining kidney substance, and as time goes on, lead through attempts at repair to a more or less chronic lesion.

I have gone into this matter somewhat critically because, although the results of reduction experiments are striking, the procedures by which they are obtained are not such as involve only a single factor, but bring several forms of kidney injury into play, that is, reduction of functional substance and productive, atrophic and vascular changes accompanied by the elimination of albumin and casts. In other words, a chronic lesion of the kidney, characterized by hypertension, heart hypertrophy and increased flow of dilute urine is produced, and this may be considered as an experimental disease analogous to certain phases of chronic renal disease in man, but it gives us no facts which explain the etiology of the vascular disturbances of the latter. The production, however, of hypertension experimentally is no small gain, and it is to be hoped that in future investigations the various factors involved in the experimental disease may be analyzed and controlled, and that the essential etiology of experimental renal hypertension established.

There is one aspect of these studies which is of considerable theoretical importance. Passler and Heineke state that although an increased flow of urine of lowered specific gravity usually accompanies the experimental heart hypertrophy, it may occur in the absence of hypertrophy and hypertension. This would indicate that polyuria is independent of

increased blood-pressure, and is of interest in connection with Loeb's hypothesis of the influence of a glomerular reflex in the production of hypertension. This is based on the frequency with which hypertension in man is accompanied by glomerular lesions (Schmidt), and on the physiological law that the functional power of the kidney depends on the rate of blood-flow through the glomerulus. Loeb assumes that with greatly increased capillary resistance within the diseased glomerulus, the increase of flow due to local vasodilatation is insufficient for the needs of the kidney, and that the glomerulus sends a call beyond the local vaso-motor system which, reaching the cerebrospinal centers, causes a reflex splanchnic vasoconstriction and thus increases the general blood-pressure so that a normal flow through the altered glomerulus results. This hypothesis might well be applied to explain the results of reduction experiments. The demands of water elimination on the greatly reduced number of glomeruli in the persisting kidney fragment might readily excite a reflex splanchnic constriction to aid in the proper elimination of water. Thus would be explained the increased blood-pressure, and by its continuance the eventual heart hypertrophy. This attractive hypothesis cannot at present receive support from reduction experiments if polyuria without increased blood-pressure, as observed by Passler and Heineke, is found to be a frequent condition. Their experiments, however, were made on a comparatively small number of animals, and the investigation of this hypothesis should be an important phase of future studies of the reduction of kidney substance.

As all forms of experimental reduction of kidney substance are characterized by loss of glomeruli and by either increased blood-pressure or polyuria, or both, and frequently by heart hypertrophy, and, on the other hand, as hypertension does not occur in the presence of a normal splanchnic circulation, it would seem possible, by properly planned reduction experiments, either to disprove or to establish Loeb's hypothesis and thus to clarify to some extent the at present confusing theories of hypertension in nephritis.

Several other aspects of this phase of renal disturbance might be discussed, as the influence of a possible internal secretion of the kidney on blood-pressure and the matter of the presence of blood-pressure-raising substances in the serum of nephritis, but to such problems the study of the acute forms of experimental nephritis has little application, and the results of the study of experimental chronic lesions, thus far obtained, are either contradictory or entirely negative.

In concluding this presentation, I admit that I have neglected several important phases of experimental renal pathology and have treated others

in a more or less incomplete way. Such omissions have been intentional, as I have preferred to emphasize those problems to which have been applied methods which offer a functional conception of disturbance in nephritis, and which tend to distinguish between the results of tubular as contrasted with glomerular lesions and to show the relation of these to some of the more important manifestations of renal disease. To such a conception, supplementing the older anatomical knowledge, we must look for the ultimate solution of the problems of nephritis.

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# A STUDY OF THE PRESPHYGMIC PERIOD OF THE HEART

G CANBY ROBINSON, M D AND GEORGE DRAPER, M D

PHILADELPHIA

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### I INTRODUCTION

The aortic valves are not opened at the very beginning of ventricular systole. The intraventricular pressure must be raised above the pressure in the aorta before the valves are opened, and in order to do this a definite, measurable length of time is required. This time is known as the presphygmic period or interval of the cardiac cycle.

The purpose of the present work has been to measure the time of this period between the beginning of ventricular contraction and the opening of the aortic valves, and to study its variations under different pathological conditions. It seemed likely that the heart would be unable to overcome the aortic pressure and so send forth the pulse wave as quickly under certain abnormal as under normal conditions, and the study was undertaken with the hope of obtaining results that would be of practical clinical value, as well as an addition to the theoretical knowledge of the pathological physiology of the circulation. Results that may prove valuable from each point of view have been obtained.

### II PRESENT KNOWLEDGE OF THE SUBJECT

The present knowledge of the length of the presphygmic period is almost exclusively confined to its normal length, and as this has been set at so many different figures, the normal presphygmic period can be considered as still unsatisfactorily measured. This period has been known by various names. It was called the presphygmic interval by Keyt, the *Anspannungzeit* or exertion time by Landois, the *Verschlusszeit* or closed period by Martius, the *Latenzzeit der Pulscurve* or latent pulse time by Edgren, and the sysasis by Garrod. All of these terms indicate a slightly different conception of the period, and but one, the *Verschlusszeit* or closed period of Martius, needs comment. Martius conceived of the period as that time when all the heart-valves are closed, a condition that is impossible when an incompetent valve is present. Our conception of the presphygmic period focuses itself on the intraventricular pressure in its relation to the intra-aortic pressure, and we think of it as that period of time during which the contracting left ventricle is raising the intraventricular pressure to overcome the intra-aortic pressure.

The presphygmic period was first measured in man by Rive, working under the direction of Donders, who determined its duration as 0.073 second. This work was followed by Landois, who gives 0.085 second for its time. Various methods have been employed for measuring the presphygmic period in man, the principal one being measuring the length of time between the beginning of ventricular systole as determined by the cardiogram, or the occurrence of the first heart tone at the apex, and the

appearance of the arterial pulse wave in some vessel, usually the carotid artery, at a point of known distance from the heart. When the time of wave transmission is subtracted from this interval, the time between the beginning of ventricular contraction and the starting of the pulse wave, the presphygmic period, remains. Tracings have also been made simultaneously from the apex-beat of the heart and from the aortic aneurisms, when the time of wave conduction can be ignored. In a few cases the presphygmic period has been measured where the human heart has been practically exposed by operative or congenital defect of the chest wall. Martius considered the ascending limb of the cardiogram as representing the presphygmic period, and he and some others have estimated its length by measuring the duration of this part of the cardiogram. The presphygmic period has also been determined by subtracting from the entire systole of the ventricle as determined by the cardiogram, that part occupied by the pouring out of blood as determined by the sphygmogram. The difference in time between the occurrence of the first heart sound at the apex of the heart and at the base has also been determined, and may represent the duration of the presphygmic period. Tigeistadt finds in his tracings from the aorta exposed by an operative procedure a small wave before the main systolic wave. This, he believes, represents the period, and measures its length as that of the presphygmic time.

Table 1 shows the results of various observers and their methods. Obviously there is little constancy in the results. This is partly due to the use of the various methods, all of which contain intrinsic errors. The chief difficulties in measuring the time between the beginning of ventricular systole as determined by the cardiogram, and the appearance of the carotid pulse as determined by a sphygmogram synchronously taken, lie in the exact determination of the foot-points of the tracings and in the correction for the wave transmission time. These two possibilities of errors will be further considered. The measurement of the interval that separates the pulsation in an aortic aneurism from the beginning of ventricular systole should be accurate, but under these circumstances the circulatory apparatus is not normal, and factors which will be shown later to alter the length of the presphygmic period are probably present. That the ascending limb of the cardiogram represents the presphygmic period has already been denied by Hilbert and others, with good reason. The tracings of Erlanger from the exposed heart have given a very long presphygmic period, or "period of rising tension," as he calls it. But he questions his own results in the measurement of this period. They were obtained by measuring the difference in time

between the beginning of ventricular systole in the cardiogram and the appearance of the pulse-wave in the brachial artery, and allowing for the time of wave transmission. A mistake in these calculations has made the time of this period about 0.015 second longer than it should be<sup>1</sup>.

An extensive study of the presphygmic period in animals is that of Hurthle. He used dogs and rabbits, and for the former gives 0.02-0.04 seconds for the duration of the period. A study of the effects of changes

TABLE 1—RESULTS OF VARIOUS OBSERVERS AND THEIR METHODS

Observer	Year of Publication	Time of Presphygmic Period in Seconds	Method
Rive	1866	0.073	Cardiogram and carotid pulse Corrected for transmission
Landois	1872	0.085	First heart tone and carotid pulse Corrected for transmission
Grunmach	1885	0.07	Not given
Keyt	1887	0.06	Cardiogram and carotid pulse Corrected for transmission
Martius	1888	0.07-0.14	Time of ascending limb of cardiogram
Edgren	1889	0.087-0.093	Cardiogram and carotid pulse, Corrected for transmission
von Ziemssen and von Maximowitch	1889	0.08-0.17	Ascending limb of cardiogram from exposed heart
Reck	1890	0.045-0.06	Cardiogram and pulsation of aortic aneurism Part of ascending limb
Hurthle	1891	0.06	Cardiogram and carotid pulse, Corrected for transmission
Hilbert	1891	0.06-0.12(?)	Cardiogram and carotid pulse, Uncorrected for transmission
Schmidt	1893	0.02-0.04	Cardiogram and carotid pulse, Corrected for transmission
Hockhaus	1893	0.07-0.10* 0.077-0.154†	Cardiogram and carotid pulse, Apparently uncorrected for transmission
Einthoven and Geluk	1894	0.06	Difference between at heart tone at apex and base
Muller	1895	0.025-0.07	Cardiogram and pulsation of aortic aneurism
Jaquet and Metzner	1901	0.02-0.03	Cardiogram from exposed heart and innominate artery Corrected for transmission
von Juergensen	1903	0.07	Not given
Erlanger	1905	0.12-0.18	Cardiogram from exposed heart and brachial pulse Corrected for transmission
Luciani	1905	0.08-0.10	Not given
Tiedestedt	1908	0.051	Tracing from exposed aorta

\* Normal † Pathological

1 At the request of Prof Erlanger we wish to call attention to an inaccuracy in calculation in his paper entitled "Cardiogram Obtained from a Case of Operative Defect in the Chest Wall" (Johns Hopkins Hospital Bulletin, 1905, xvii, 394). In estimating the time of transmission from the base of the heart to a point 35 cm distant on the brachial artery, he says that as the rate of transmission in the brachio-radial artery of this case was 6.8 meters per second, the delay, or time of pulse wave transmission was 1.8 divisions of his time marker, which recorded 0.02 seconds, or 0.036 seconds. The proper time of pulse wave transmission is 0.0515 or approximately 2.5 divisions of the time marker.

in aortic pressure and of various stimulations are included in his work. Marey measured the period in the horse, and found it to be 0.01 second, while Friederiq gives 0.07 second for the dog.

### III METHOD OF PRESENT STUDY

The present investigation of the presphygmic period is based on a study of about sixty patients, from whom between six and seven hundred tracings were made. Over 500 of these tracings were studied, but only about 200, representing 20 of the 60 patients, were used as a basis for conclusions. As much care as possible was exercised to exclude faulty or wrongly interpreted tracings. The method employed consisted in taking a series of tracings from each patient from the apex-beat of the heart, carotid, brachial and radial arteries and from the jugular vein, in various combinations. The difference in time between the beginning of ventricular systole and the appearance of the carotid pulse (the V<sub>s</sub>-C time) was measured from the curves. The speed of pulse-wave transmission was measured in the brachial and radial arteries by taking tracings synchronously from two points on the arm at a known distance apart. By this means the speed of wave transmission per centimeter in each patient was determined, and this was multiplied by the distance from the second right interspace on the chest wall to the point where the carotid tracing was obtained. By this means the time of wave transmission from the aortic valves to the carotid artery (S-C or semilunar—carotid—time), was determined. By subtracting the S-C time from the V<sub>s</sub>-C time, that is, subtracting the time of wave transmission from the time between the beginning of ventricular systole and the appearance of the carotid pulse, we obtain the presphygmic period. The time between the ventricular systole and the appearance of the radial pulse-wave, the V<sub>s</sub>-R time, was measured to obtain a controlling factor. The jugular pulse tracings were used to aid in the interpretation of the cardiograms. Although the method is simple, it contains both inherent inaccuracies and technical difficulties. In order to minimize the effects of these difficulties tracings were, in all cases that were finally used, taken two or more times until an agreement of results occurred. The tracings were taken by the Jaquet sphygmocardiograph, with which, after considerable practice, satisfactory curves were obtained. The double lever action of the writing levers, the benefits of which have been recently pointed out by Petter, and the horizontal rather than vertical movement of the writing-points, are both features of the instrument that make it preferable to the usual types of drum kymograph. Of course, the convenience of its application and its portability make it very suitable for clinical use.

The time relation of two curves synchronously taken was always measured by that part of the time-marking curve that lay directly above the measured interval. The time-curve marked intervals of 0.2 second. All measurements were made from curves taken when the instrument was running at its faster speed, i.e., the paper moving at about 10 cm per second. The tracings from the radial artery were obtained by spring transmission, as arranged in the Jacquet instrument. The receiving apparatus for all other curves was except in special instances, an open funnel, with air transmission. The cardiograms were usually made with the patient lying slightly on the left side.

The results from only those tracings which fulfilled the following conditions were used. In each curve the following conditions must be fulfilled:

1. The beginning points of all waves (foot-points) must be sufficiently sharp to ensure their accurate determination.

2. The waves must all be of approximately the same size, contain no signs of technical deformity and represent as nearly as possible the full motion of the vessel or heart.

3. The distance between the points where the writing levers rest at the beginning and end of a curve must be the same in the three synchronously taken tracings. This was to prove that the paper had run straight through the apparatus.

To calculate time relations, the relations of all synchronous waves in a tracing that fulfilled the above conditions were measured, and when these measurements all fell within the limit of technical error, they were averaged. After many observations the limit of technical error has been considered as 0.010 second.

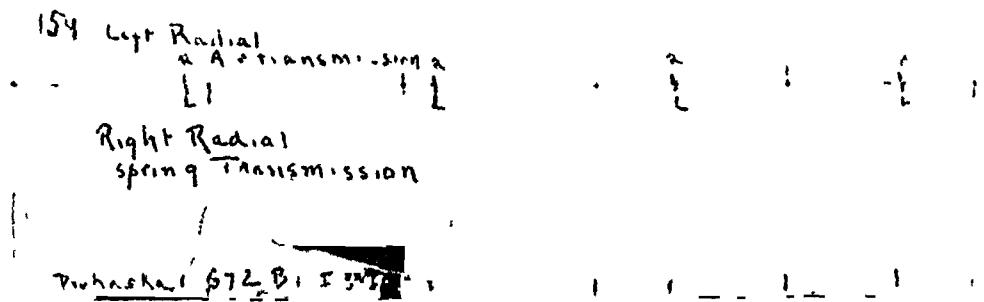
#### IV CRITICISM OF METHOD

The presphygmic period can be studied in a relatively small percentage of cases, for unless there is some cause to produce overaction of the heart, or unless there is some abnormality which allows unusual exposure of the heart, it is very difficult to obtain cardiograms satisfactory for study. Therefore determination of the normal presphygmic period is especially difficult. The inherent inaccuracies of the method make it impossible to measure the length of the presphygmic period with mathematical correctness. The aim has been to come as near this as possible, and to keep all sources of error constant, so that variations are real.

It is impossible to determine exactly the transmission time of the pulse-wave from the aortic valves to the carotid artery, because the speed of

wave transmission in this stretch of vessels can not be directly measured. Nor does it seem correct to consider this time a constant in all cases, as has been done by several previous investigators, since the extensive work of Keyt shows that many factors may change the speed of wave transmission, and since Grunmach gives figures to show that pathological conditions may produce these changes. So it was considered more nearly approaching accuracy to determine the speed of pulse-wave transmission per centimeter in the vessels of the arm in each case, and to calculate the S-C time with this unit. For this purpose, tracings were taken from the right brachial artery at an average distance of about 40 cm above the wrist synchronously with tracings taken from the left radial artery. From these tracings the speed per centimeter in the arteries of the arm was obtained by dividing the total time intervening between the brachial and radial wave by the distance separating the receivers.

The three possible sources of error in this method are that there may be differences in transmission by the spring and air methods, that the



Tracing 1—Treadings from both radial arteries (from Case 9) left with air transmission, right with spring transmission showing that the waves are recorded synchronously

pulses in the two arms may not be synchronous and that the speed of wave travel may not be, and is probably not the same, up to the carotid artery as it is along the arm

The first of these possible sources of error was eliminated by the following procedure. Curves were taken from the two radial pulses, synchronously, one by the usual spring transmission and the other by a specially devised receiver with air transmission and without the use of any spring. The two receiving methods were then reversed and the spring transmission applied to the right wrist instead of to the left as at first and vice versa with the air transmission. Under both conditions the pulse waves fell accurately together (Tracing 1). This result shows not only that the two methods of transmission are of equal speed, but that the radial pulses were in the two cases in which this experiment was made,

synchronous Excellent curves by Keyt in several instances show that the radial pulses are normally synchronous

In a number of cases tracings were made from the radial and brachial artery synchronously on the same arm This method always gave a slower speed of wave travel than when the crossed method (brachial tracing from one arm and the radial tracing from the other) was used, so that it was considered that pressure exerted on the brachial artery caused a delay of the pulse-wave below this point Keyt has shown that this is true Therefore, the crossed method was considered more accurate The two radial pulses were always palpated together to determine as far as possible whether they were synchronous or not The effect of slowing of wave-speed due to pressure may possibly account for the much slower speed obtained by practically all other observers An attempt was made to devise a formula by which the speed of wave transmission in the arm vessels could be corrected for the vessels leading to the neck, but this was not possible, and the speed of wave transmission as found in the arm arteries was applied to determine the time of transmission to the carotid artery It is not easy to say whether this procedure makes the S-C transmission too long or too short The question of wave transmission in the various vessels is a very complicated one It has been recently discussed by Nicolai, who says that speed of wave travel must be greater in the aorta than in the arm vessels, and it is more rational to believe that the pulse-wave travels at a more rapid rate up to the carotid from the heart than it does along the arm arteries If this be the case our correction for transmission has been too great Grunmach, on the other hand, gives figures that indicate that the speed of pulse-wave travel is less up to the carotid than it is along the arm arteries His methods deserve criticism, however He measured the time between the appearance of the carotid wave after the beginning of the apex-beat in synchronously taken tracings, and assuming that the presphygmic period was a constant, subtracted 0.07 from this time The results of our work show that this assumption was not warranted, and so it may have led to inaccurate results He gives no tracings from which to judge of his curve interpretation Keyt's thorough consideration of this point led him to a definite conclusion that the pulse-wave travelled slowest in the aorta, and if his results as obtained on a constructed scheme of tubes and pump can be applied to the living organism, his conception is surely correct

It seems more likely that the pulse-wave travels up to the carotid artery more slowly than it does along the arm, and therefore more time should have been subtracted from the V<sub>s</sub>-C time than we have taken to get the correct time of the presphygmic period

The determination of the speed of wave transmission in the arm by the methods which we have employed cannot be considered entirely satisfactory. At first tracings were taken from the brachial artery by the application of a well-fitting rubber-rimmed receiver, but with the hope of obtaining better results in the last ten cases the turgosphygmograph of Kozieckowsky was employed, as well as the funnel receiver. Kozieckowsky's instrument did not prove very satisfactory for our purpose, and in only three of the ten cases were better curves obtained with it than with the funnel receiver (Tracings 2 and 3). The average speed of wave transmission in the arm as obtained by the funnel receiver over the brachial artery was 11.13 meters per second while with the turgosphygmograph it was 16.16 meters per second. As the tracings from the radial artery remained a constant, the method that gave the slower transmission speed must be considered the better as it is the method which recorded the earlier wave impulse in the brachial artery. For a stretch of 40 cm of vessel about the length usually employed the average transmission time



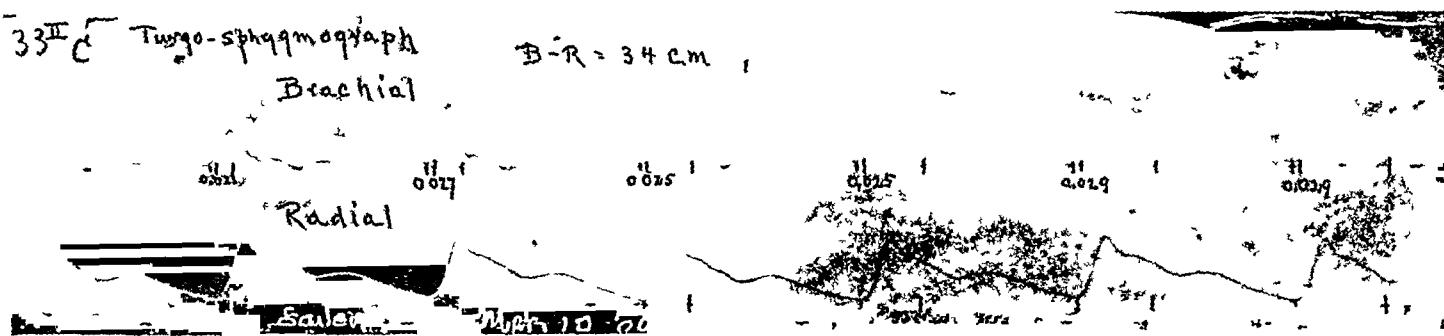
Tracing 2—Curves from brachial and radial arteries, brachial tracing obtained by funnel receiver (Case 18)

with the funnel transmission was 0.028 seconds and for the turgosphygmograph 0.024 seconds. The extremes of transmission speed that were employed in the calculations were from 8.35 meters to 20.0 meters per second. This transmission time is distinctly faster than the figures given by others. Eilanger gives 6.8 meters per second in the brachial and radial arteries, Grunmach, 6.15 meters per second from the heart to the radial pulse, Huithle, 6 meters per second Landois 9.42 meters per second in the arm arteries, and Jaquet and Metzner 5.33 between the innominate and the carotid arteries.

We have preferred, however, to take the figures as we have found them in each case, rather than to adopt from the figures of others a standard of wave transmission for all cases. Although we feel that correction of transmission time from the semilunar valves to the carotid artery is not

mathematically correct, we believe that we have approached accuracy as closely as possible, and that the error must cause such a small inaccuracy in the calculated time of the presphygmic period that it can be practically ignored. The speed of wave transmission in the arm, together with the presphygmic period and diagnosis is given in Table 2.

A number of technical difficulties which were found to lead to incorrect results had to be carefully guarded against. It was found that the smoked paper strip could run through the Jaquet instrument obliquely, so that the distances between the points where the various writing levers rested before starting and after stopping the instrument were not the same in the three synchronously taken curves. Indeed, the distortion could be so marked that when the point of departure of the measuring compasses was taken at the beginning of the strips one set of wave relations resulted, while, when the point of departure was taken from the terminus and the strip measured backward a totally different wave relation was obtained. Vigilance was always necessary that mistakes might



Tracing 3—Curves from brachial and radial arteries, brachial tracing obtained by turgosphygmograph

not occur in the many measurements and calculations that were necessary.

But the chief difficulty was found in determining the exact position of the foot-point or beginning point of the various curves, and in deciding when the foot-point actually represented the beginning of the various movements in vessels or heart. A simple rule that aided in the interpretation of curves was the following. Any error in the foot-point in the first of two synchronous waves tends to lessen, any error in the foot-point of the second tends to lengthen the distance between the foot-points of the two waves. It was often especially difficult to know when the tracing from the carotid artery showed the first movement of that vessel. The importance of determining that point is illustrated by Diagram 1. When the funnels or pelotte were not properly placed

over the vessels, or when the vessels were so deep-lying that proper application was difficult, the waves were sometimes preceded by a definite dip or negative influence, which, of course, made accurate determination of the proper foot-point impossible. In other tracings the rising limb of the curves was preceded by a flat base, which indicated that the receiver was not resting on the vessel, and was not at all times recording the movements of the vessel. In one tracing from the carotid artery a marked anacrotic wave was present in the first waves, but had nearly disappeared before the end of the tracing. With the disappearance of this wave the tracing would have become quite inaccurate. It may be readily supposed that through thickened arterial walls the pulse-wave would not be conveyed so quickly as through soft, relaxed walls, and that so great a pressure could be put on a vessel, especially on the radial artery by the spring of the sphygmograph, that time would be lost in overcoming this pressure before the writing lever would be moved. It is possible also

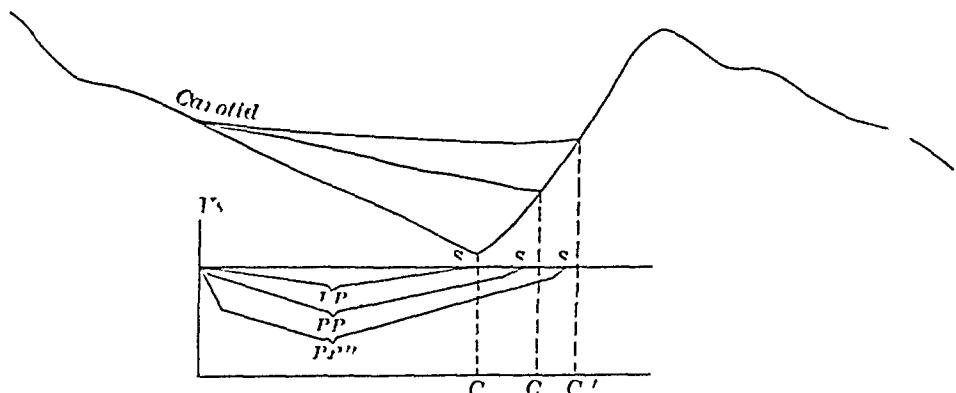


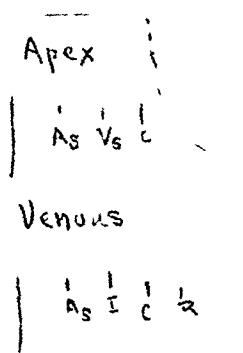
Diagram 1.—True (c) and false (c' and c'') foot points of carotid wave, showing how its incorrect determination may alter the measurement of the presphygmic period (P P, P P and P P''). V, indicates relatively where foot point of cardiogram would fall.

that too thickly smoked paper can interfere with the movements of the writing levers. All of these faults of technic have been kept in mind, and when any of them was detected the tracing was not used.

Considerable study and practice was necessary in order to determine successfully the beginning of ventricular systole from the cardiogram. That this point can be determined accurately from cardiograms is indicated from an observation by Hurthle, who took synchronously tracings from within the left ventricle of a dog by means of a sound, and a cardiogram from the chest wall, and found that the beginning of ventricular systole was indicated at the same time by both tracings. The exact determination from the human cardiograms often presents a difficulty which Martius and some others have overcome by graphically recording the first

heart tone at the apex and making measurements from this point. In one of our cases where this was done by means of the heart-tone capsule of Frank, the first tone was found to begin slightly later than the first movement of ventricular systole.

A very important factor in the interpretation of the cardiogram is the presence of the wave caused by the auricular systole, the so-called  $A_s$  wave or "auricular flip." Our experience confirms Muller's statement that if no  $A_s$  wave appears, the foot-point of the  $V_s$  wave is uncertain. Exceptions to this rule are found in cases with paralysis of the auricle or when the  $A_s$  and  $V_s$  are not properly coordinated. Another reason why the  $A_s$  wave is important is that it practically assures that the heart is against the anterior chest wall at the beginning of ventricular systole, and that the first effects of ventricular systole are recorded.

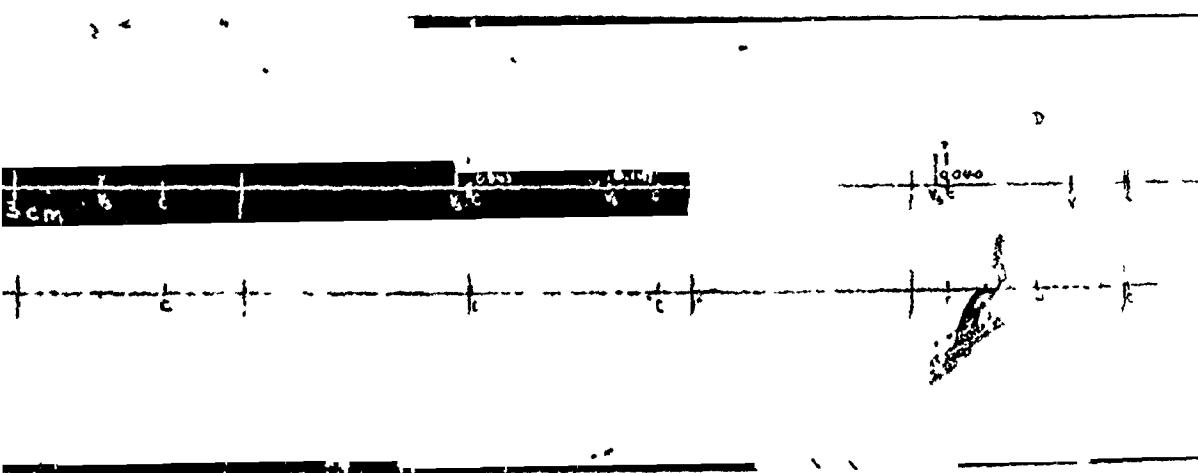


Tracing 4—Showing  $A_s$  wave of the cardiogram in its more perfect form, the first part negative and the second a positive wave. The I wave is also shown and is seen to be synchronous with the I wave in the jugular tracing (Case 21).

The  $A_s$  wave of the cardiogram may vary considerably in form and relation to the  $V_s$  wave without there being any dissociation of the heart beat. Wenckebach has pointed out that the  $A_s$  wave is a pulse phenomenon when positive and due to the muscular action of the auricle when negative. The two are often combined, the negative part, which is often not seen, occurring first, and the positive wave occurring later. This we believe to be the more perfect form of  $A_s$  wave (Tracing 4), and this consideration of it explains why the  $A_s$  wave of the venous pulse may occur synchronously or before the  $A_s$  wave of the cardiogram, when only the positive part of the wave is seen in the cardiogram. The  $A_s$  wave at times is distinctly separated from the  $V_s$  wave (Tracing 5), while at other times it lies high on the cardiogram and may mask the beginning of the  $V_s$ .

wave (Tracing 6). In some of Erlanger's tracings from the exposed heart the A<sub>s</sub> and V<sub>s</sub> waves are nearly merged into one and form an almost unbroken ascending line. As that author remarks, it is therefore obvious that under certain circumstances the two curves might be actually indistinguishably merged. In such a case it would be impossible to determine from a study of the ventricular cardiogram alone the moment of the beginning of the ventricular contraction. Muller has also noted the possible confusion between the A<sub>s</sub> and V<sub>s</sub> waves.

There is another wave which occurs not infrequently in the first part of the cardiogram, and which may be readily confused with the A<sub>s</sub> wave. It may vary in position even as much as the A<sub>s</sub> wave, but usually occupies when present the lower half of the ascending limb of the cardiogram. It may lie, however, along the base line of the cardiogram in a horizontal manner. Then it is especially easy to confuse it with the A<sub>s</sub> wave. This

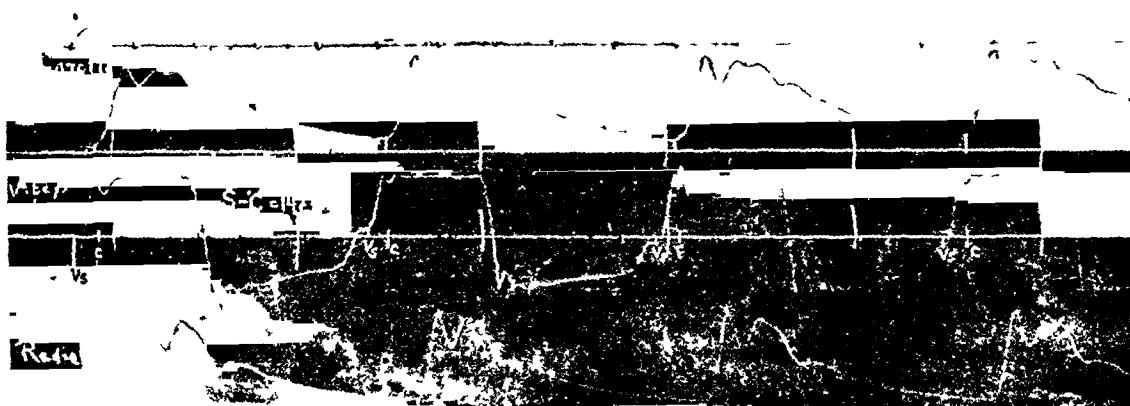


Tracing 5.—The A<sub>s</sub> wave is seen distinctly separated from the V<sub>s</sub> wave. Bigeminal pulse. The first cardiogram of the pair shows very short V<sub>s</sub> C time, the second a very long one (Case 8).

confusion has been recently referred to by Pachon. This wave was present in various forms in four of our twenty-one cases. As it lies between the A<sub>s</sub> wave and the main V<sub>s</sub> wave, we shall call it "I" wave. It corresponds, at least in time, with the I wave of the venous pulse (B wave of Piersol) [Tracing 4]. The significance of this wave has been discussed by Jacquet and Metzner, who believe that it is part of the V<sub>s</sub> wave, but they come to no conclusions as to its cause. Tigeistadt offers the following explanation for the intersystolic wave. Through auricular contraction the ventricular walls are expanded, and then contract through their elasticity before systole begins. By this means the pressure in the ventricle is raised above that of the auricle, and the auriculoventricular valves

are closed before the  $V_s$  begins. Thus is the intersystole formed. Piersol has considered this wave as representing the presphygmic period. This conception will be referred to later. We believe, however, with Jaquet and Metzner that the I wave is part of ventricular systole. Pachon offers experimental evidence for the same conclusion. We have found that sometimes the occurrence of this wave is markedly influenced by the position of the patient, and that it is more prominent when the patient lies on his back than when he is on the left side (Tracings 7 and 8). In some cardiograms both the  $A_s$  wave and the I wave are seen (Tracings 4 and 9). In Tracing 9 the two waves are especially well seen in their most common forms. The relation between this wave and the presphygmic period will be spoken of later.

It is in distinguishing the  $A_s$  wave from the I wave of the cardiogram that the jugular pulse tracings have proved of especial value. Such trac-



Tracing 6.—The high-standing  $A_s$  wave which may mask the beginning of  $V_s$  is seen (Case 3)

ings were made in all cases in which it was possible, and where these failed in several cases we were aided in the interpretation of cardiograms by tracings made by Dr Edens from the left auricle through the esophagus. It is practically always possible to distinguish the  $A_s$  wave from the I wave by the jugular or esophageal tracings, and therefore the foot-point of the cardiogram is made much more certain. It is likely that these waves have been confused by some who have worked previously with cardiograms and that some statements of Schmidt may be attributed to this error.

In cases giving unusual cardiograms, the new photographic kymograph of Frank was employed and curves were obtained that were of distinct aid in determining the exact foot-points.

TABLE II—CASES IN ORDER STUDIED

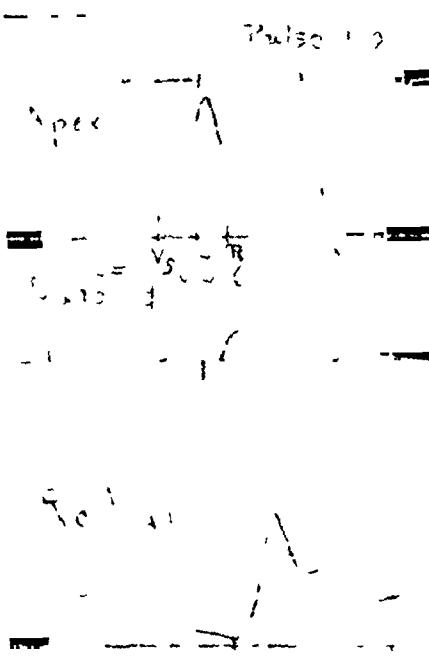
No of Case Subject	Age of Case Subject	Diagnosis	V <sub>S</sub> C Time	Speed Per cm	S-C Time	P <sub>co</sub> sphygmic Period	S-R Time	Blood-pressure mm Hg	Pulse-Rate	Curve No
1	60	Atherosclerosis	0.016	0.00067	0.0092	0.015	0.084	125—70	93	6
2	22	Laryngitis	0.082	0.00085	0.012	0.07	0.091	58	7	7
3	26	Aortic and mitral insuff., syphilis	0.080	0.00098	0.014	0.066	0.104	154—	62	8
4	25	Aortic and mitral insuff., aortic stenosis?	0.125	0.00095	0.017	0.108	0.099	110—	87	9
5	34	Aortic and mitral insuff.	0.110	0.0009	0.016	0.094	0.084	122—70	73	10
6	61	Gout and polyarthritides	0.096	0.0008	0.013	0.083	0.078	115—90	88	11
7	18	Articular rheumatism	0.098	0.00115	0.016	0.082	0.113	110—90	81	11
8	71	Atherosclerosis, myocarditis, arrhythmia?	0.041	0.00067	0.008	0.011	0.012	218—95	19—64	11
9	44	Aortic insuff., coronary sclerosis, syphilis	0.102	0.00075	0.011	0.093	0.064	110—95	79	15
10	22	Pharyngitis, bronchitis, neuasthenia	0.074	0.00062	0.010	0.064	0.060	110—70	81—100	16
11	21	Pneumitis	0.092	0.0006	0.009	0.082	0.078	110—70	72	19
12	23	Chronic nephritis	0.096	0.0005	0.007	0.089	0.082	100—130	55	22
13	28	Chronic nephritis	0.119	0.0009	0.011	0.105	0.073	115—115	70	23
14	41	Aortic insufficiency	0.080	0.0009	0.014	0.066	0.098	125—	100	27
15	20	Articular rheumatism	0.096	0.0006	0.008	0.083	0.087	130—100	88	28
16	60	Myocarditis, anemia, arteriosclerosis	0.038	0.0008	0.008	0.039	0.036	115—105	78—107	31
17	40	Mitral insuff. and stenosis, aortic insuff., arrhythmia	0.123	0.0008	0.010	0.113	0.089	180—100	67—78	32
18	39	Myelogenous leukemia, mitral insuff.	0.177	0.0006	0.009	0.059	0.067	95—60	74	33
19	24	Aortic and mitral insuff., arrhythmia	0.104	0.00087	0.013	0.091	0.077	98—55	74	34
20	22	Myocarditis, arrhythmia, artificial rheumatism	0.127	0.00105	0.010	0.070	0.069	110—70	54—71	34
21	23	Neuasthenia, neurotic arrhythmia	0.119	0.00052	0.008	0.064	0.077	95—50	55—69	37
			0.080	0.0007	0.010	0.070	0.085	115—70	76	41

## V RESULTS OF PRESENT STUDY

By the employment of the foregoing methods, and by using only curves of whose interpretation we felt sure, we believe that we have greatly minimized or eliminated the error that would arise from a false interpretation of cardiograms or from the use of faulty cardiograms. We believe that, in all cases from which conclusions have been drawn, we have definitely determined the point of beginning of ventricular systole.

The gross results of this work can be tabulated as in Table 2.

In Table 2 the cases are arranged according to the order in which they were studied. All time measurements are in seconds. The V<sub>s</sub>-C time is the average time (except where two figures are given) that the begin-



Tracing 7—I wave absent, tracing taken with patient lying on left side (Case 10), showing one of the shorter V<sub>s</sub>-C times from case of neurotic instability of the heart. See Tracing 13.

ning of the pulse wave appeared at a certain point in the carotid artery after the beginning of ventricular systole as indicated by the cardiogram. This point in the carotid artery averaged about 15 cm from the second right interspace. It was the point where the pulse could best be recorded, and, of course, varied in different individuals. The speed per centimeter is the speed per centimeter of pulse-wave travel in the brachial and radial arteries. The S-C time is the calculated transmission time from the semilunar valves to the point in the carotid artery. This subtracted from the V<sub>s</sub>-C time gives the presphygmic period. The S-R time is

the calculated time of wave transmission from the semilunar valves to the radial artery. This is obtained by subtracting the presphygmic time from the V-R time, and is of value only as a control, especially on the speed of wave transmission.

Although this table shows the details of our findings, a better idea of the normal length of the presphygmic period, the variations in its length and relation to other circulatory variables can be obtained from a table in which the cases are arranged according to the increasing lengths of the presphygmic period (Table 3).

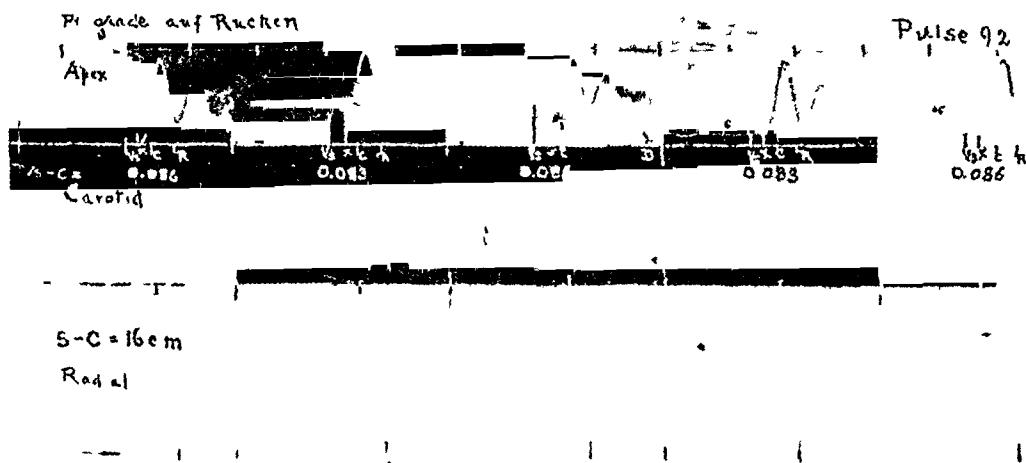
TABLE 3—CASES ARRANGED ACCORDING TO INCREASING LENGTHS OF PRESPHYGMIC PERIOD

Presphygmic Period	No. of Case	Diagnosis	Blood Pressure mm Hg	Pulse Rate Per Minute	Speed of Wave Transmission, Meters Per Second
0.032—(0.111)	16	Myocarditis, paroxysms of tachycardia, arrhythmia, arteriosclerosis	S—180 D—100	78—107	12.5
0.033—(0.088)	8	Arteriosclerosis, myocarditis	S—218 D—95	48—64	15.5
0.036	1	Arteriosclerosis	S—125 D—70	93	14.7
0.061—(0.082)	10	Neurasthenia, bronchitis and pharyngitis	S—130 D—70	83—100	16.1
0.064—(0.111)	20	Myocarditis, arrhythmia, rheumatism	S—95 D—50	62	20.0
0.066	.	Aortic and mitral insufficiency, syphilis	S—151 D—	62	9.9
0.066	11	Aortic insufficiency, syphilis	S—125 D—	100	11.8
0.070	2	Laryngitis		78	11.8
0.070	21	Neurasthenia, neurotic arrhythmia	S—115 B—7	70	14.3
0.070—(0.117)	19	Aortic and mitral insufficiency, arrhythmia	S—110 D—70	74—71	15.6
0.080	11	Pleuritis	S—110 D—70	52	16.6
0.082	7	Articular rheumatism	S—130 D—90	47	8.7
0.083	6	Gout and polyarthritides	S—135 D—90	88	12.5
0.088	15	Articular rheumatism	S—130 D—100	88	17.7
0.089	12	Chronic nephritis	S—190 D—130	55	20.0
0.089—(0.168)	17	Mitral and aortic insufficiency, mitral stenosis, auricular fibrillation, arrhythmia	S—95 D—60	67—78	15.2
0.091	18	Myelogenous leukemia, mitral insufficiency (?)	S—98 D—75	74	11.8
0.091	9	Aortic insuff., coronary sclerosis, syphilis	S—130 D—95	79	13.4
0.094	5	Aortic and mitral insufficiency	S—122 D—70	70	11.1
0.105	13	Chronic nephritis	S—145 D—115	78	11.2
0.108	4	Aortic and mitral insufficiency, aortic stenosis (?)	S—110 D—	73	10.5

The normal presphygmic period is not easily determined, not only on account of the fact that it is nearly impossible to measure it in perfectly healthy individuals, but also because from a series such as ours it is very difficult to determine where the abnormal merges into the normal, and vice versa. But it is evident that those figures lying in the middle of our series represent more nearly the normal than do the extremes. We believe that the normal presphygmic period has a duration of from 0.07 to 0.085 seconds, but, as has been said previously, this cannot be considered more than relatively correct, and not of absolute mathematical accuracy.

riacy. The normal length of the presphygmic period is the duration of that period in a subject who possesses sound heart and arteries which are under a healthy, normal nervous control. That diseases of the heart and vessels and a deranged nervous control may be present without changing the presphygmic period beyond its normal limits cannot be denied. But we believe that whenever we have found that the presphygmic period departs from these limits that it has always been the result of some circulatory abnormality. Pathological conditions may cause the presphygmic period to be shortened and to be lengthened, and when factors producing both changes are present, it is probable that they may balance each other, and so produce no change sufficiently great to pass the limits of normal.

Cases 2, 6, 7, 11 and 21, with diagnoses of laryngitis, neurasthenia, pleuritis, articular rheumatism and gout and polycythemia, showed nearly



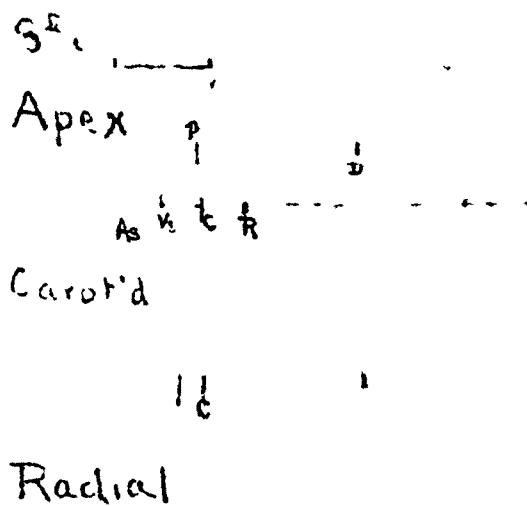
Tracing 8.—Tracing from same patient (Case 10) as Tracing 7, I wave well seen. Patient was lying flat on his back. X is placed at end of I wave.

normal hearts and vessels. Their presphygmic periods all fell within the limits of 0.07 second and 0.085 second. These times were, therefore, considered as the nearest to normal of all the cases studied.

Cases 3 and 14, which lie just below the set limit, showed distinctly deranged circulations, while Cases 15, 12, 19 and 9, with nearly similar presphygmic periods lying just above the limit, also showed circulatory abnormalities.

The variations in blood-pressure do not bear the relation to the variations in the presphygmic period that is rationally expected. The figures in Table 2 show no apparent relation between the length of the period and the amount of either the systolic or the diastolic pressure. The blood-pressure was determined by the Riva-Rocci sphygmomanometer.

with the auscultatory method. It must be remembered, however, that the only measurable diastolic pressure is the mean pressure. The end diastolic pressure is significant in the rôle which blood-pressure plays in determining the length of the presphygmic period. This, of course, cannot be measured in man. There does seem, however, to be some relation between the short presphygmic period of the first two cases and the large difference between the systolic and diastolic pressures, the blood-pressure amplitude. This condition of blood-pressure, combined with arteriosclerosis is we believe, the probable cause of the short periods. This will be further discussed. That there is otherwise no apparent relation accords with the experimental findings of Hunthlie. He raised the aortic blood-pressure in dogs by direct pressure, and instead of producing a



Tracing 9—A<sub>s</sub> and I waves both well seen in their most common forms (Case 3)

lengthened period, as was expected, he found that there was at least a tendency for the presphygmic period to be shorter with the higher than with the lower initial-aortic pressure, thus affording an example of the wonderful accommodating power of the circulatory apparatus.

The pulse-rate in various cases bears no apparent relation to the lengths of the presphygmic periods. Although no satisfactory curves bearing on the question of the effect of changes in the pulse-rate in the same individual have been obtained, our evidence seems to indicate that the length of the period does not change with the pulse-rate to the extent

Keyt believed it to do. We believe also that Garrod is in error when he says that the period decreases in length as the pulse increases in rate, so that when the beats are 170 per minute the length of the period is reduced to nothing. Indeed, the experiments of Hurthle on dogs give contrary evidence. He varied the heart-rate by vagus stimulation without producing variations in the length of the presphygmic period. We feel that the relation to the changes in the heart-rate is an unsettled question.

The speed of wave transmission as measured in the arteries of the arm bears no apparent relation to the duration of the period (Table 2).

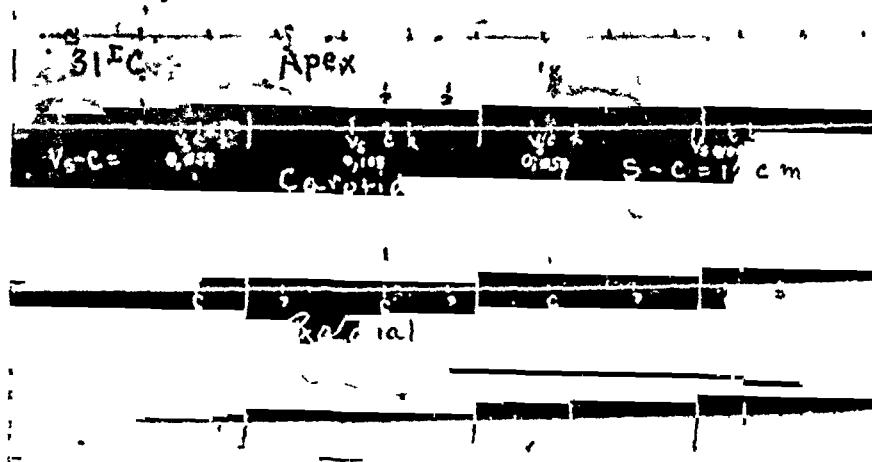
The relation of valvular heart disease to the length of the presphygmic period is of especial interest, and we have studied aortic insufficiency and mitral insufficiency from this point of view. The effect of valvular lesions has been studied by Hilbert, Hochhaus, and especially by Keyt. Hilbert estimated the period in five cases of aortic insufficiency, pure and combined with other lesions, and concludes that in hearts in good compensation the presphygmic period is not altered by insufficient aortic valves. Hochhaus gives the length of the period for groups of pathological conditions. He found that the average time for six cases of mitral insufficiency was 0.093 second. He considers 0.07 to 0.10 as the normal time, and says that in six cases of mitral stenosis the variations were within normal limits. In two cases of uncomplicated valvular disease with arrhythmia, lengthening was present. The extensive study of Keyt on the effect of valvular lesions, both on the presphygmic period of man and of an artificial heart and circulatory apparatus, led him to conclude that marked aortic insufficiency produced great shortening and mitral insufficiency lengthening of the period. He believed that these facts had very important diagnostic value. Although his tracings are in the main excellent, his reasoning correct and his point of view entirely rational, his conclusions are borne out by our findings only in part.

As first pointed out by Keyt, a theoretical consideration of mitral insufficiency would lead to a belief that this lesion causes a lengthening of the presphygmic period. The rush of blood backward into the auricle during systole would make it more difficult for the ventricle to raise the intraventricular pressure, and therefore it would be expected that a longer time than normal would be required to overcome the intra-aortic pressure.

In aortic insufficiency however, the constant communication between the aorta and the left ventricle tends to lessen the differences of pressure that are present at the end of diastole, and so the intra-aortic pressure should be overcome quickly. When the aortic valves are practically absent, a condition that probably almost never occurs Keyt believes that the V<sub>s</sub>-C time is reduced to the transmission time, as the column of

blood of the aorta rests on the ventricular walls instead of on the aortic valves. These theoretical considerations do not seem to hold true for the circulatory apparatus of man as they do for the artificial heart and vessels.

We have encountered too few cases of uncombined valvular lesions to draw definite conclusions. Of the eight cases which were judged clinically to have incompetent valves, two showed a shortened and six showed a lengthened presphygmic period. The cases of shortened period both had aortic insufficiency, one pure and one combined with mitral insufficiency. Five other cases with aortic insufficiency combined with other lesions, showed lengthened periods. In the two cases it seems very likely that the shortened presphygmic period was the effect of the aortic insufficiency. Where the period was not shortened other factors especially the mitral insufficiency may have offset the effect of the aortic insufficiency.

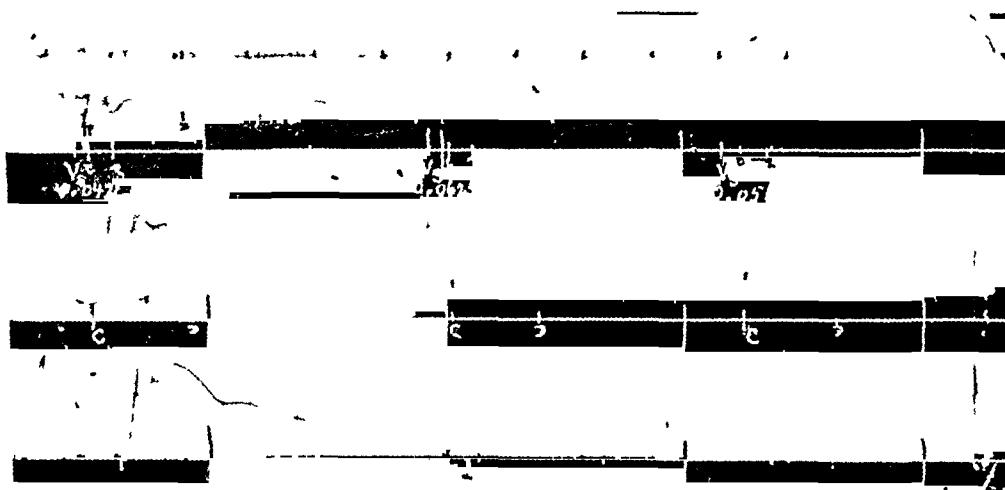


Tracing 10—Showing short V<sub>s</sub>-C time

After coordinating the clinical study of the cases, when signs of lack of functional capability were especially considered, we believe that the abnormal length of the presphygmic period depends more on the lack of ability of the heart to meet the demands on it than it does on valvular lesions in themselves. Weight is given to this suggestion by the findings in two incompletely studied cases. The first was a case of pure mitral insufficiency in which there were definite signs of decompensation. The average V<sub>s</sub>-C time was 0.111 second, which would give a presphygmic period of about 0.10, a marked lengthening. In the other case there was pure mitral insufficiency without decompensation. The average V<sub>s</sub>-C time was 0.066 second, and the presphygmic period can be assumed at about 0.056 second, or distinctly under the normal limits. In

these two cases lesions giving similar cardiac murmurs were present, while there was a marked difference in the ability of the two hearts to meet the vital needs, and we believe that it was more the difference in the general condition of the circulatory apparatus due to the combination of abnormalities than it was the valvular lesions alone that produced the marked differences in the presphygmic times. It is difficult, however, to say just what rôle the valvular lesions as such play in producing variations. As the study of the two foregoing cases was not completed, they have not been used in our series. One patient became so ill that it seemed advisable to repeat the tracings, and so to control our figures, and the second patient left the hospital before the second tracings could be made.

Arteriosclerotic changes in the circulatory apparatus appear to have a marked tendency to shorten the presphygmic time. Five of the seven cases which have a presphygmic time below what has been taken to be the



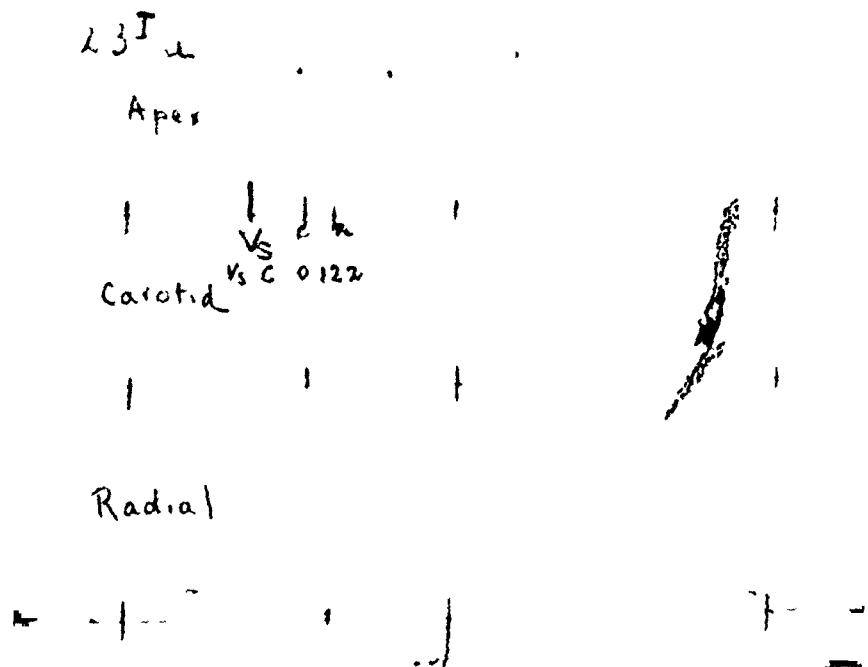
marked arrhythmia with varying V<sub>s</sub>-C time (Case 16)

normal limit, give grounds for believing that the arteries were diseased. The two exceptions, Nos 10 and 20, were cases of arrhythmia which had only occasionally presphygmic periods of slightly shorter duration than the normal time, undoubtedly due to factors other than arteriosclerosis. The three cases of outspoken arteriosclerosis that were studied, Nos 16, 8 and 1, are the three that show the shortest presphygmic time. Two of these cases, it is true, were arrhythmic, and in them much longer periods than these lower limits were usually seen, but the hearts in both cases under certain conditions were capable of having presphygmic times markedly less than the lower normal limit (Tracings 5 and 10).

The two cases, Nos 3 and 14, which showed presphygmic times just below the normal limits, in spite of the fact that the hearts were not

entirely capable functionally, and showed aortic insufficiency, were syphilitics. It may be therefore, that conditions approaching those found in the arterial sclerotic cases were present and may have been a factor in shortening the period.

As has already been suggested, it seems likely that the shortening of this period in arteriosclerosis bears some relation to the large blood-pressure amplitude. It is necessary for the heart to contract forcibly in order to overcome the peripheral resistance produced by inelastic arteries. This lack of elasticity probably deprives the vessels of their accommodating power and prevents them from contracting as readily as normal vessels in order to maintain the blood-pressure. Owing to this lack of contractility of the vessels the pressure in the larger arteries drops



Tracing 11—Showing long V<sub>s</sub> C time, compensation good (Case 13)

suddenly after the pulse-wave has passed, and a low diastolic pressure is produced. In arteriosclerotic cases there is present, therefore, a strongly acting left ventricle, overcoming a low end-diastolic intia-aortic pressure, thus producing a short presphygmic period. It does not seem clear why in one case a very short period occurs without a large blood-pressure amplitude, although it seems quite reasonable to suppose that with loss of elasticity in the circulatory apparatus, the opening of the valves would occur more suddenly and sharply.

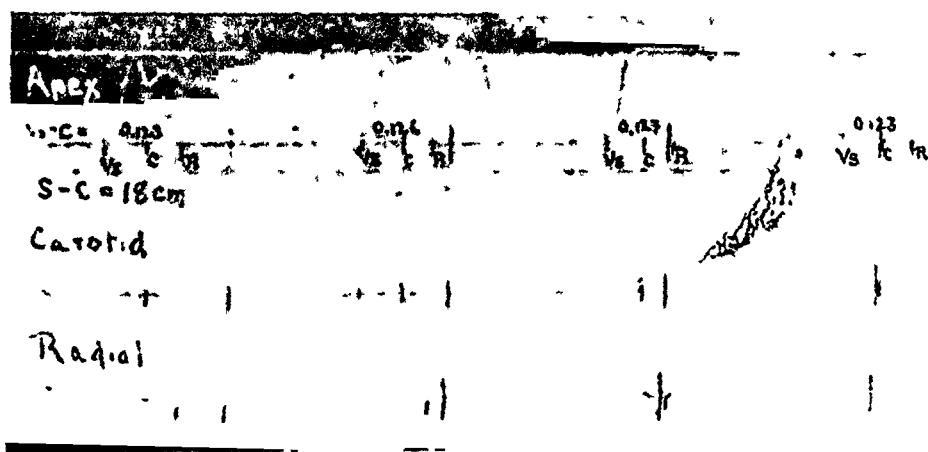
Lengthening of the presphygmic time was always present in each of the eight cases that showed various forms of circulatory disturbances. The

case lying just above the normal limit was a youth of 20, who suffered from articular rheumatism, and who showed no signs of cardiac disease other than a persistently overacting and somewhat rapidly beating heart. The presphygmic time was 0.088 second. As the cases lying below this one in Table 2 are reviewed, and the clinical study of them coordinated with the length of the presphygmic period, it is seen that the hearts in these cases as a rule apparently decreased in efficiency as the presphygmic period lengthened. The two exceptions to the rule are Cases 17 and 13. The former showed a heart distinctly deficient in functional capacity, and the presphygmic time under the most favorable circumstances was only 0.089 second. Under certain other conditions, however, the extremely long time of 0.168 second was encountered. If the average time had been used for classification instead of the shortest that occurred, this case would stand much lower in the list. Case 13 had a much longer presphygmic period than would be expected from the clinical findings. The heart was somewhat enlarged, but generally no murmurs were heard, and the compensation seemed good. We believe that it is possible that there was more severe muscular weakness than could be detected by the usual methods of examination, or that in some manner the accommodation of the heart was so deranged that the high diastolic blood-pressure of 115 mm Hg had a marked influence on the length of the presphygmic period (Tracing 11). This idea suggests that the method that we have used may give valuable information about the real power of the heart, but of course much more extensive work must be done before any conclusions on this point can be drawn. Case 4, which gave the longest period in the series, showed signs of poor compensation and the circulatory apparatus was perhaps in a worse condition than that of any of the other cases, as judged from clinical findings (Tracing 12).

The presphygmic period was studied in one case which showed a condition of the circulation which may be termed neurotic instability, No. 10. The term is applied to that class of cases which show signs of vasomotor instability, usually a rapid heart, but readily changing in rate, and showing no apparent arrhythmia, the condition of the circulation so frequently seen in highly neurotic individuals. The heart is often overacting, but may be free from organic disease. In this case the average length of the period in various curves varied from 0.064 to 0.082 second. Six sets of curves were made at intervals through a period of two weeks, and all the tracings were especially scrutinized for defects. The presphygmic time did not vary from beat to beat of the heart, but was so constant on each occasion that all the measurements from one tracing could be averaged, although those from all the sets of tracings could not

The pulse-rate varied between 72 and 100 per minute, and there was a tendency for the shorter presphygmic times to occur with the faster pulse-rates but this relation was not constant. The heart gave no signs of organic disease and although it was overacting, the orthodiagram showed that it was not enlarged. At times the presphygmic time fell below the lower normal limit for which fact we have no explanation. The variations in the lengths of the presphygmic period in this case of a highly neurotic individual were certainly real and not associated with any detectable technical error (Tracings 7 and 13). The possibility suggests itself that like the readily varying pulse-frequency the changing presphygmic period was a manifestation of the nervous instability or excitability of the circulatory apparatus.

The changes in the presphygmic period that occurred in certain forms of cardiac arrhythmia were very striking, and in the same patient the



Tracing 12—Showing long V, C time compensation bad (Case 4)

priesphygmic time may be more than three times as long with one systole as with another. This variation has been pointed out by Hochhaus, whose tables show in a rather indefinite way that the length of the period seems to depend on the length of the preceding diastole. Lewis has recently mentioned the fact that the priesphygmic period may be lengthened after a short diastole in an extrasystole, and he points out an error into which Mackenzie seems to have fallen by overlooking this fact in measuring the A-C time in the venous pulse in cases of arrhythmia. Rehberg has also remarked on the probable variations in the priesphygmic period in cardiac arrhythmia.

We have obtained satisfactory curves in four cases which showed marked cardiac arrhythmia Nos 8, 16, 17 and 19, associated with marked irregularities in the presphygmic time. In Case 8 the period

varied in time from 0.033 to 0.088 second, although in some other weak systoles, in which the time could not be accurately measured, the presphygmic time was about 0.140 second. The form of arrhythmia was of the extrasystole type, and this long period is seen in an extrasystole where the heart was beating so as to give a bigeminal pulse (Tracing 5). The short time of 0.033 was seen in cardiograms, which were the first of two contractions when the heart was acting bigeminally. When the heart was acting regularly, under which conditions five sets of tracings were made, the presphygmic time was found to be from 0.05 to 0.07 second, but was a constant in each of the several curves. The cause of the shortening in this case has been already discussed, when the effect of the arteriosclerosis was under consideration.

Pulse 82.

$$16^{\text{IV}} \alpha$$

Apex

$$V_s - c = \frac{V_s}{0.097} \text{ sec}$$

Carotid

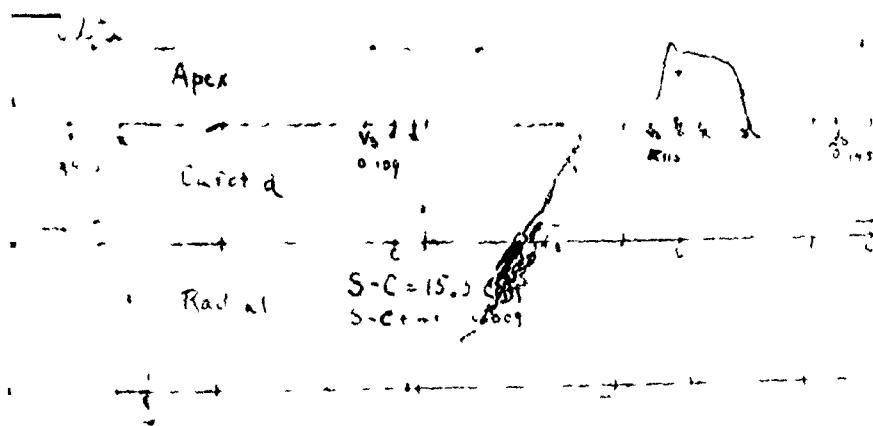
R. radial

Tracing 13—Showing one of the longer  $V_s - c$  times from case of neurotic instability of the heart (Case 10). Compare with Tracing 7 from same case showing one of the shorter  $V_s - c$  times.

In Case 16 the presphygmic time varied from 0.032 to 0.113 second. The patient was a woman, aged 60, with a systolic blood pressure of 180 mm Hg, and a diastolic pressure of 100. The heart was enlarged especially to the right, there was a systolic murmur at the apex, fairly marked arteriosclerosis and marked arrhythmia of the pulsus irregularis perpetuus type. Tracings made from the jugular veins and from the esophagus by Dr Edens gave no evidence of auricular contractions (Tracing 10).

Patient 17 was a woman, aged 10, whose blood pressure was S-95 and D-60, and whose heart was distinctly enlarged to both the right and left. A systolic and diastolic murmur was heard at the apex and a diastolic murmur was heard over the lower part of the sternum. Clinically she was considered to have mitral stenosis and mitral and aortic insufficiency. There was marked arrhythmia, and the jugular and esophageal tracings indicated the same type of arrhythmia as the preceding case. Variations in the presphygmic time from 0.092 to 0.168 second have been encountered in the same tracing (Tracings 14 and 15).

Patient 20 was a man of 22 who was suffering with acute articular rheumatism. The heart was distinctly enlarged, especially to the left, its border being 15 cm from the midsternal line. No murmurs were present, but a protodiastolic gallop rhythm was heard at times. Blood-pressure was S-1, 95 I-D 50. There was usually present a marked arrhyth-

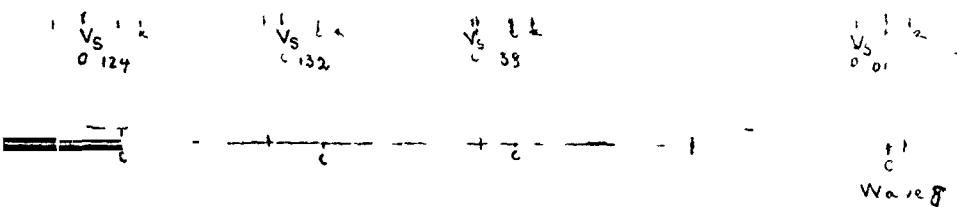


Tracing 14—Showing marked arrhyth-

mia. The analysis of the venous tracings and those obtained from within the esophagus showed a disturbance in conductivity which was sufficient to allow independent ventricular systoles at times thus producing arrhythmia of the ventricles. When the heart was acting irregularly, the presphygmic time varied from 0.064 to 0.111 second. One week after taking the curves showing irregularities, other curves were made when the heart was quite regular, pulse 55 per minute and a presphygmic period of 0.067 or slightly below what has been considered the normal limit was found. At this time the venous pulse was entirely normal.

All the four cases in the foregoing group present arrhythmia apparently dependent on some cause other than the nervous control of the heart. A very striking feature of all these cases is that the variations in the time of the presphygmic period bear an almost constant relation in

each case to the length of the preceding diastole. The longer the diastole the shorter the presphygmic period of the systole that immediately follows it. That this relation is not an absolute constant seems to depend on the fact that it is influenced by factors other than the length of diastole. But generally speaking it may be said that in cases of arrhythmia such as have been described the length of the presphygmic period depends on the amount of rest the heart has had in the preceding diastole and the condition in which it is when ventricular systole begins. Of course, the end diastolic pressure is also a determining factor in the length of the presphygmic period, and it may be lower after a long diastole than after a short one, and so play a rôle in the presphygmic variations. In Table 4 the presphygmic time of the various systoles of Curve 32a (Tracings 14 and 15) from Case 17 are set down according to their increasing length, together with duration of the preceding diastole and of the dura-



with varying V<sub>s</sub>-C time (Case 17)

tion and strength of the preceding systole. The strength of the preceding systole can be approximated only by the size and length of the systolic part of the pulse curve that it produces in the carotid sphygmogram, a somewhat unreliable method. The method of measuring the lengths of systoles and diastoles will be discussed later.

The relation between the lengths of diastole and of the presphygmic period in the foregoing table are seen in Chart 1, where the length of the presphygmic period is used as the ordinate, and the length of diastole as the abscissa.

#### VI SIGNIFICANCE OF VARIATIONS IN THE PRESPHYGMIC TIME

It is seen from Table 4 that the combination producing the shortest presphygmic period is a long diastole preceded by a weak systole, as in Wave 8, Tracing 14, and that a short diastole preceded by a strong sys-

TABLE 4—PRESPHYGMIC TIME OF VARIOUS SYSTOLES OF CURVE 32 IA

No. of Wave	Presphygmic Time in Seconds	Time of Preceding Diastole	Time of Preceding Systole	Strength of Preceding Systole
7	0.092	0.990	0.368	Weak
10	0.100	0.803	0.389	Weak
1	0.100	0.675		Fairly Strong
8	0.103			
2	0.106	0.694	0.387	Strong
13	0.106	0.599	0.358	Weak
4	0.115	0.385	0.367	Weak
5	0.123	0.233	0.365	Weak
6	0.127	0.228	0.360	Weak
12	0.135	0.228	0.348	Weak
3	0.136	0.339	0.370	Strong
11	0.146	0.252	0.378	Strong
9	0.168	0.220	0.370	Fairly Strong

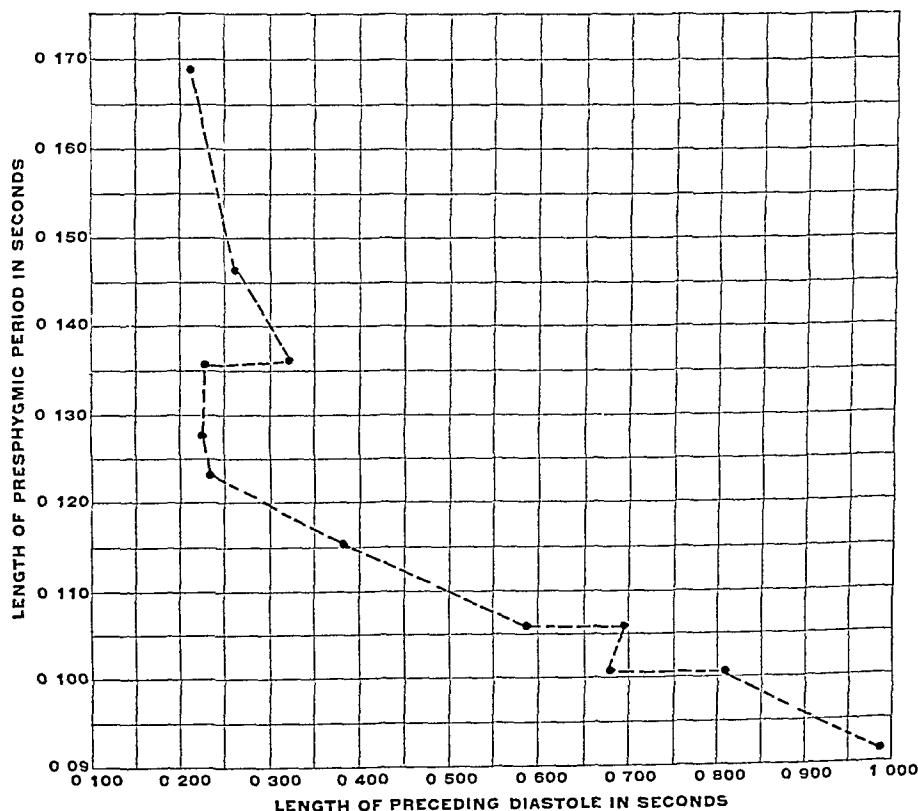
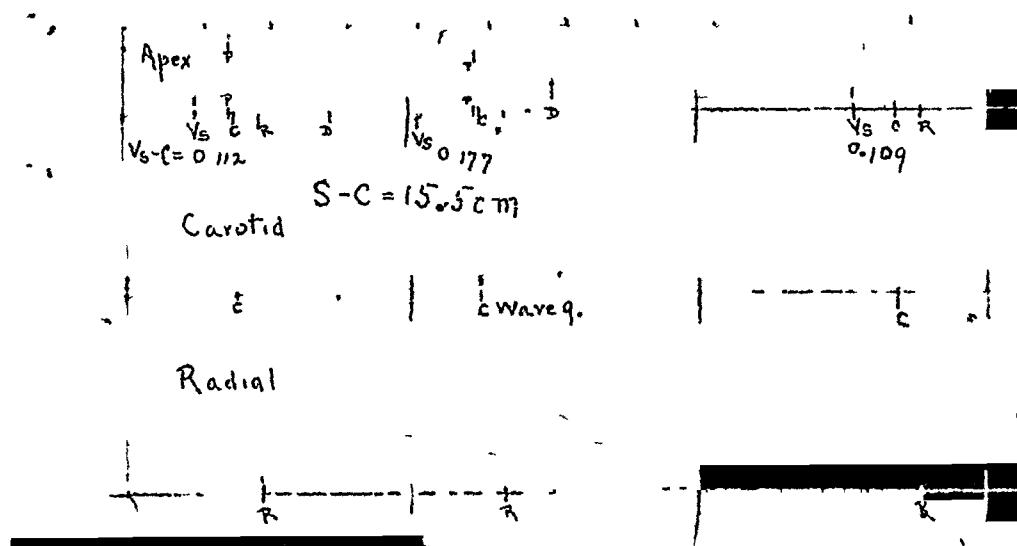


Chart 1—Curve plotted from relative lengths of diastoles and succeeding presphygmic periods in Case 17

tole, as in Wave 9, Tracing 15, produces the longer presphygmic time. That the strength of a systole plays a rôle in the length of the presphygmic period of the following systole was suggested by all our tracings from these cases of arrhythmia. Whenever it is found that a comparatively short diastole is followed by a systole with a relatively short presphygmic period, the curves from the carotid artery show that the systole previous produced a sphygmogram whose systolic portion was both smaller in amplitude and shorter in length than normally. This form of sphygmogram indicates, we believe, a weak systole. Let us express this idea somewhat more extensively. It seems that the length of the presphygmic period affords a measure of the force of ventricular systole. Then it follows that if the length of the preceding diastole governed alone the force of the succeeding systole, the presphygmic periods following dia-



Tracing 15—Showing marked arrhythmia with varying presphygmic period (Case 17), part of same curve as Tracing 14 and showing very long V<sub>s</sub>-C time

toles of the same length would be always equal. But this is not the case, and the irregularity depends apparently on the force of the preceding systole. For the curves indicate that, even when the diastoles are of equal length, the presphygmic period of a systole that comes after a preceding weak systole is shorter than that of the systole that comes after a preceding strong one. It appears that after a weak systole there may be two factors which shorten the presphygmic period. On the one hand, the heart is not so fatigued as after a strong contraction, and so attains a higher state of efficiency during the same period of rest, while on the other hand the end of diastolic pressure may be lower after a weak contraction than after a strong one. The effect of a weak systole is brought out in

a curve from Case 17 and is shown in Diagram 2, which has been schematically constructed from the tracings from two consecutive cardiac cycles. Here it is seen that, in spite of the fact that in Wave 7 the diastole is longer than in Wave 8, the presphygmic period is also longer. This apparent irregularity seems to depend on the difference in the force

Systole	Diastole	P P
S 0.376	D 0.289	P 0.144

Wave 7

Systole	Diastole	P P
S 0.342	D 0.252	P 0.133

Wave 8

Diagram 2—Constructed from two consecutive waves of Curve 32IIa (not shown in tracings) Showing that length of systole also has an influence on the following presphygmic period

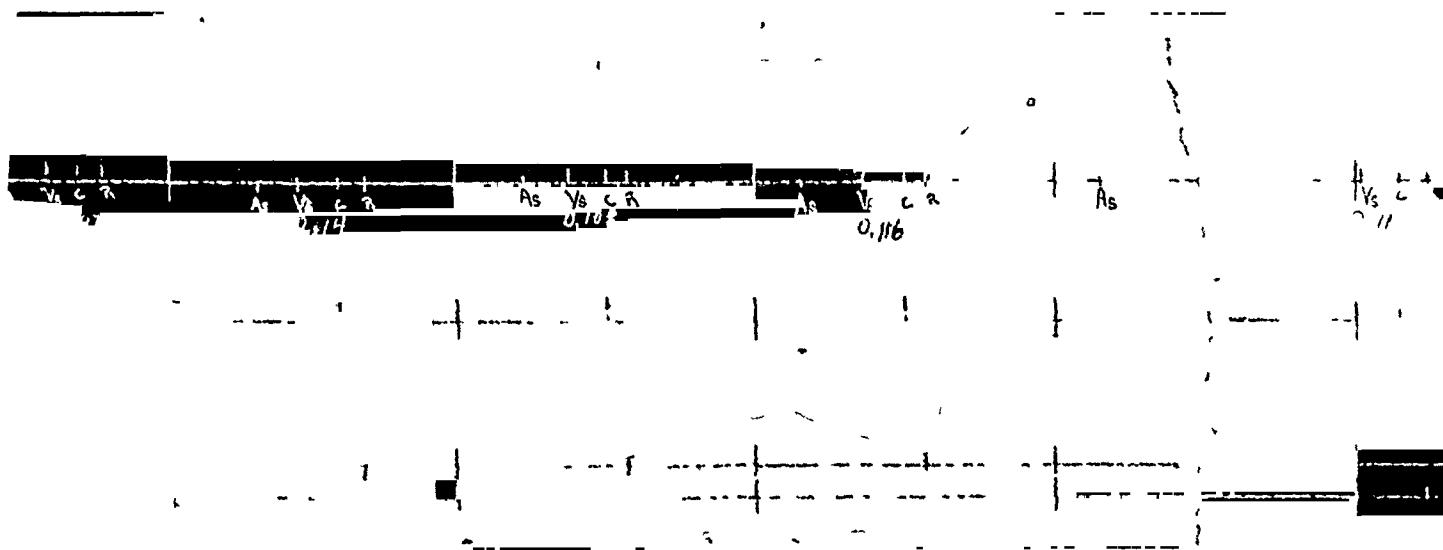
Tracing 16—Rhythmic dissociation of  $A_s$  and  $V_s$  waves seen in card

of the preceding systole, as the difference in the lengths of diastole cannot account for it

These facts have a bearing on the ideas expressed by Langendorff in regard to the constancy of heart work. He says that, since the pause that follows an extrasystole is longer than it would have been without the extrasystole, a greater amount of energy is stored up than would have occurred normally. The stored-up energy is entirely freed at the next systole, and the amount that is, therefore, lost depends on the size of the preceding extrasystole and on the length of the pause (diastole). Langendorff says that the recording of the increase in shortening of the heart muscle (apparently his method) is not a satisfactory means of obtaining some information in regard to the working capacity of the heart, and so

our confirmation by another method of estimating the working capacity of the heart seems important

The question must be considered whether changes in rate of wave transmission also take place in these cases of arrhythmia, and so make variations in the  $V_s$ -C time greater than is due to the presphygmic variations alone. That the transmission speed of the pulse-wave remains a constant is seen from the calculated S-R time, obtained by subtracting the presphygmic time from the  $V_s$ -R time, or the time of wave transmission from the semilunar valves to the radial artery. This time is found to be almost a constant in all curves, and the slight variations that are seen in it bear no relation to the length of the presphygmic period. This may be illustrated by Table 5, in which the P P and S-R times are given from Curve 31 Ia



shows lack of relation between  $V_s$ -C time and length of diastole in spite of arrhythmia

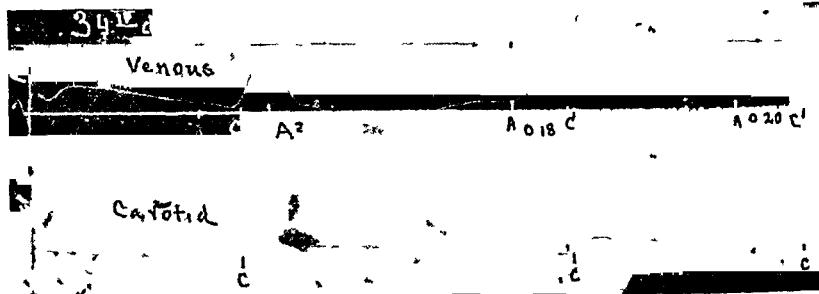
TABLE 5—P P and S-R TIMES FROM CURVE 31 IA\*

No of Systole	P P Time	S R Time
1	0.070	0.086
2	0.113	0.087
3	0.040	0.085
4	0.061	0.079
5	0.053	0.086
6	0.051	0.081

\* It is seen that in this series the S R times do not vary beyond the limit of technical error of 0.010

It may, therefore, be said that all changes in the  $V_s$ -C time are due to variations in the presphygmic period, and are not dependent in any way on changes in the speed of wave transmission.

Some of the tracings from these cases of arrhythmia show well-marked cardiograms, formed by systoles that produce no or almost no impression in the curves from the carotid and radial arteries. Under such circumstances the longest presphygmic period is found. This suggested that a so-called frustrated systole may be considered the presphygmic phase of a cardiac contraction which produces no sphygmic phase. Under such circumstances the longest possible presphygmic period would be produced (See seventh cardiogram, Tracing 10). Hochhaus has discussed the subject of frustrated systoles and gives evidence to show that ventricular systoles do occur which fail to open the aortic valves. He and Quincke believe that such systoles are due to muscle weakness and represent a qualitative change. This agrees with our idea that in these arrhythmias the length of the presphygmic period depends on the relative strength or force of the ventricle when systole begins.

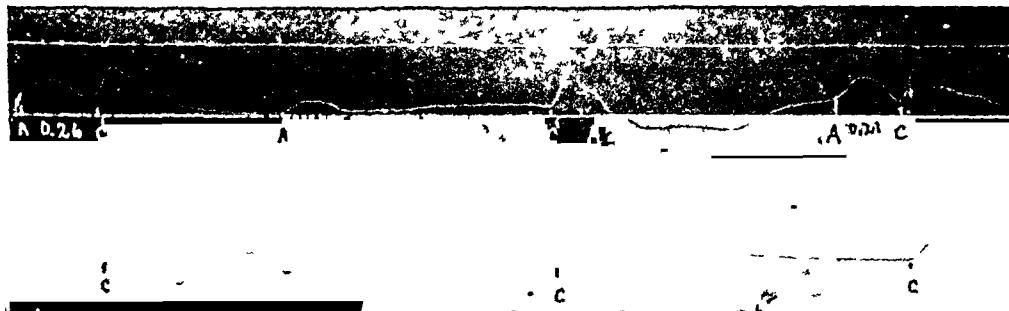


Tracing 17 — Venous pulse tracing

Changes in the presphygmic period do not depend on arrhythmia alone. Two cases were encountered in which any changes in the presphygmic time that occurred were entirely independent of the arrhythmia, i.e., bore no relation to the length of the preceding diastole. These were Cases 19 and 21. The first patient was a young man of 24, who was in the hospital for acute articular rheumatism. At the time when we studied him he had entirely recovered from the symptoms of rheumatism. His heart was slightly enlarged and acted forcibly. There was a systolic murmur at the apex, pulmonic and aortic areas, and a diastolic murmur heard in a small area in the third left interspace at the sternal border. He was considered to have mitral and aortic insufficiency, myocarditis (?) and showed marked arrhythmia at times. The blood-pressure was S-100, D-70, and the pulse varied from 54 to 71 per minute. When the patient was out of bed, in conversation or under any condition of general excitement, the pulse was more rapid and entirely regular. When he was lying quietly in bed and after the application of an ice-bag

to the precordium, the heart became slower and showed marked arrhythmia. The application of the ice-bag seemed to be the principal factor in producing the arrhythmia, which appeared usually from fifteen minutes to half an hour after its use was begun. Most of the six sets of tracings made from this patient were taken while he showed cardiac arrhythmia.

The arrhythmia was of an especially interesting and unusual variety. From the cardiograms, the jugular pulse curves and the esophageal tracings, a rhythmic dissociation was seen (Tracings 16 and 17). At one point in the curves the  $A_s$  and  $V_s$  waves hold a normal relation. At the next contraction the  $A_s$  and  $V_s$  waves are somewhat separated, and at the third still more separated. This increase of separation of the  $A_s$  and  $V_s$  waves continues for four or five beats when the  $A_s$  wave fails to be followed by a  $V_s$  wave. Then the ventricle contracts through its own rhythmicity, the rate of which was 34 per minute, and the regular auricu-

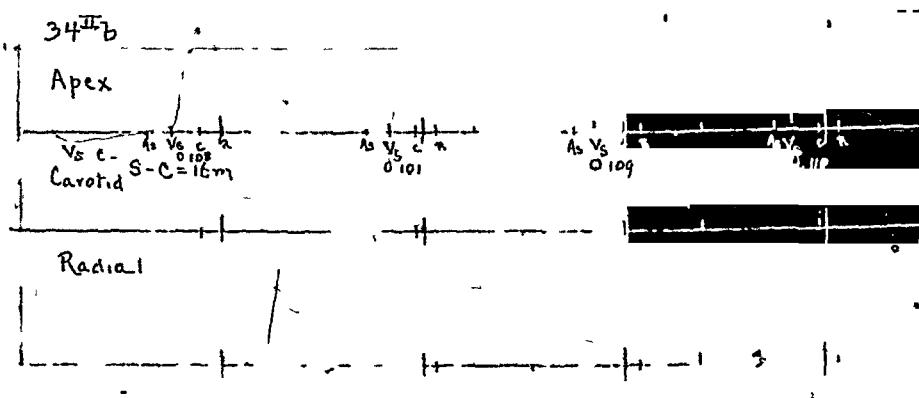


same case as above (Case 19)

lar systole occurs synchronously with it, the two practically always falling together or the  $V_s$  following the  $A_s$  so closely that these waves are nearly always merged. Slight separation was seen in the jugular tracings at times. After the apparently independent contraction of the ventricle for usually one, sometimes for two beats, the normal relation of  $A_s$  and  $V_s$  waves is resumed, to be followed by a series of cardiac cycles similar to those described. When the heart is beating regularly and more rapidly, the venous tracings are entirely normal, there is no lengthening of the A-C time, and no tendency to dissociation is seen (Tracing 18).

Earlier, when the patient was suffering with the articular symptoms of acute rheumatism, the cardiac disturbances were studied by Dr Edens. After the administration of digitalis an arrhythmia occurred, which, tracings showed, was due to complete dissociation of auricles and ventricles. This arrhythmia disappeared with the use of atropin, and showed all the features of so-called digitalis heart-block.

At the time when we studied the case, several weeks later, a striking feature was the method of production of the arrhythmia. When the heart was acting rapidly no abnormal alteration of the heart-beat was present, a fact which suggests that the disturbance was not a common one of conductivity (dromotropic). We believe that the arrhythmia was more probably due to a depression of the excitability or stimulability of the ventricles, a bathmotropic disturbance, although the possibility of it being a disturbance of conductivity cannot be excluded. It seems likely that under the influence of quiet and of the application of ice to the precordium the stimulability or *Reizbarkeit* became so depressed or the resistance to stimulation, the *Reizschwelle*, became so raised that the stimulation from the auricle was effective normally in the ventricles only after the ventricles had gone through a period of abnormal rest. This period of rest was obtained during the long ventricular diastoles formed



Tracing 18—Tracing from same case (Case 19) as Tracings 16 and 17 when heart action was regular

by the failure of the ventricles to respond to the auricular stimulation. After this rest the ventricles responded normally for one or two beats as a rule, but this response gradually became slower until the auricular stimulation failed to be effectual, and another period of rest due to a dropped ventricular systole occurred. During this prolonged rest probably the stimulability or possibly the conductivity of the ventricles was raised, while the pulse and the curves indicated no increased contractile force of the left ventricle.

We see perhaps in this case some indication why the application of ice to the precordium has a beneficial effect in certain forms of cardiac disturbances, which depend on the overactivity of certain cardiac properties.

To return to the effect of the arrhythmia in this case on the presphygmic time. We were surprised to find, after having studied the other cases of arrhythmia, that here no relation existed between the length of diastole and the presphygmic time. This lack of relation may be readily seen in Table 6, where the times of diastoles are arranged according to their increasing lengths and followed by the length of the presphygmic time of the next systole.

TABLE 6.—TIMES OF DIASTOLES ACCORDING TO THEIR INCREASING LENGTHS \*

No. of Wave	Time of Diastole in Seconds	Time of Following Presphygmic Period
10	0.418	0.094
4	0.421	0.091
9	0.423	0.089
5	0.435	0.094
1	0.491	0.098
6	0.513	0.098
8	0.743	0.089
3	0.793	0.089
2	1.048	0.088
7	1.275	0.087

\* The table is made from Tracing 34 Ic (not shown in the illustrations). It is seen that although there are slight variations in the presphygmic time, they bear no relation to the great variations in the length of diastole.

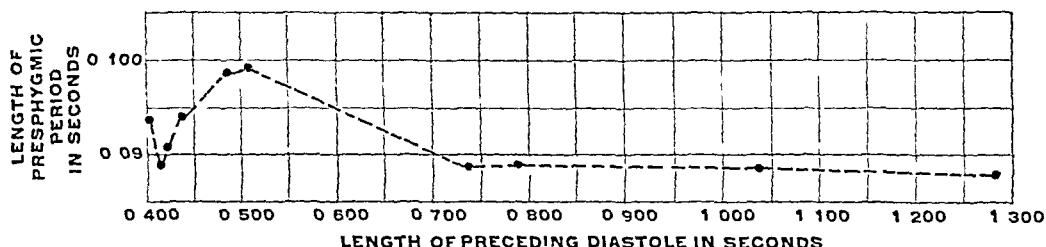


Chart 2.—Curve plotted from relative lengths of diastoles and succeeding presphygmic periods in Case 19.

The figures of this table have been used to construct Chart 2 in the same manner as Chart 1 was constructed, to which it forms a marked contrast.

Tracings taken from this patient when the heart was acting regularly gave an average presphygmic time of 0.094 second, a fact which led us to believe that under these circumstances the heart did not possess a normal amount of functional capacity. In the many tracings taken in this case there was a fairly large variation in the presphygmic time. The shortest time observed was 0.070 second and the longest 0.117. The average time

of the different curves taken in different days also varied, the shortest average time was 0.092 and the longest 0.106 second. As no relation between the arrhythmia and the length of the presphygmic time can be established, we are unable to explain this variation on any other ground than considering that it belongs in the same group as the cases showing neurotic instability of the circulatory apparatus. It was observed, however, that on the day when the heart was acting most irregularly the average presphygmic time as determined on three separate curves was longer than at any other time.

The second case of arrhythmia, No. 21, which showed a practically constant presphygmic time, was that of a man of 23, who was very neurotic, but who, in spite of a moderate arrhythmia, showed no physical signs of cardiac abnormalities. The length of the diastoles varied from 0.373 second to 0.551, while the presphygmic period remained sufficiently constant, so that all figures from two sets of tracings could be averaged, and had a duration of 0.70 second. The venous pulse curve in this case was normal, and the case was apparently one of pure neurotic arrhythmia.

#### VII POSSIBLE PROGNOSTIC VALUE OF MEASUREMENT OF THE PRESPHYGMIC TIME

Cases of cardiac arrhythmia may be divided therefore, into two groups, according to whether the presphygmic period varies with the cardiac irregularities, or whether it does not. Since the length of the presphygmic period seems to afford a measure of the force of ventricular contraction, it may be said that in the first group of cases, according to the variations in the presphygmic period, the force of ventricular systole varies. This was corroborated by the general appearance of the curves and the feel of the pulse. In the second group of cases the force of ventricular contraction remained constant. It appears that in the first group some accommodating power of the heart is lost which is present in the other group. It is difficult to say in what this power consists but in the cases in which it is lost the heart muscle seems to be distinctly more diseased than in the other cases. The two factors governing the length of the presphygmic period are the speed at which the intraventricular pressure is raised and the height to which this pressure must be raised in order to overcome the intra-aortic pressure at the end of diastole. This intra-aortic pressure cannot be measured from beat to beat. It seems likely, however, that after a longer diastole this pressure is lower than after a shorter. No matter what these changes are, the hearts in the group with the constant period are able to contract in such a way that the left ventricle overcomes the intra-aortic pressure in a constant length of time in each

beat without being influenced by the length of the preceding diastole. The heart contracts in such a way that the action of the left ventricle meets the vital needs in a constant manner. In the other group of cases this does not occur, and under certain conditions of improper rest the cardiac action is such that the left ventricle opens the aortic valves only after a delay or under certain conditions (frustrated systoles) fails to do so. In the group of cases with the varying period the left ventricle seems to gather contractile force throughout the whole of diastole, while in the other group even the shortest diastoles seem of sufficient length to allow the ventricle to gather enough force to overcome the probably varying intra-aortic pressure in a constant length of time. In this group of cases, however, very short diastoles are not seen. The difference in the two groups of cases seems to lie in this fact, the first group with the varying period gathers contractile force throughout the whole of the diastoles, no matter what their length, while the second group gathers sufficient force during the first part of each diastole, and this store of energy is not added to beyond a certain point, no matter how long the diastoles continue.

Hering has pointed out that in the heart muscle an exact balance between assimilation and dissimilation exists, thus preventing fatigue, which does not occur as long as no disturbance in either of these activities is present. It seems likely that disturbances in these functions are present in those cases of arrhythmia showing variations in the length of the presphygmic period, while they are not present in the second group of cases. The first group seems to depend for its peculiarities on disturbances inherent in the heart muscle itself, while the second group is more likely associated with disturbances in the nervous control of the heart. Our present knowledge of the control and mechanism of the heart-beat does not allow a certain separation of these functions. To say that arrhythmias showing variations in the length of the presphygmic period are of muscular origin would probably lead us into error, for Hochhaus believes that frustrated systoles (the systolic contractions that show the longest possible presphygmic time) can come through nervous disturbances alone. Hoffman is quoted as believing that nervous disturbances are the most probable cause of frustrated systoles. An arrhythmia which produces changes in the presphygmic period, however, is probably a severer form and of worse prognostic significance than an arrhythmia with a constant presphygmic period.

The significance of variations in the presphygmic period is a question which cannot be answered as yet with any degree of assurance. It is certain that the presphygmic time differs in different individuals and that it

may depart from the normal by being either shorter or longer. And it is certain that it may vary in the same individual in different cardiac systoles. The process of measuring it is not without difficulties or errors, so that as a clinical procedure on which to base conclusions in regard to any particular patient it is as yet, of course, of limited value. The fact that pathological conditions may shorten as well as lengthen its time makes judgment as to the significance of its variations difficult. Those changes of the circulatory apparatus, of which arteriosclerosis is a part, which cause shortening of the period, must be considered as tending to offset changes in the opposite direction. With a better understanding of the rôle that various factors play in producing changes in the presphygmic time, especially those which tend to shorten the time, it may be found that in this procedure of measuring the duration of the presphygmic period we have a means of determining the capability of the heart regardless of the lesions or functional disturbances that may be present. Further work is required before an opinion of value can be expressed on this question, and to determine the prognostic significance of variations of the period it will be necessary to follow the progress of cases, coördinating clinical data with the changes in the presphygmic time.

As has been mentioned under the question of the effect of valvular disease, there seems to be a fairly definite relation between the state of compensation and the length of the presphygmic time. That the period is long in cases of broken compensation seems very probable. This fact has led to the idea that in hearts in which compensation is broken and the muscle by rapid and tumultuous contractions can barely meet the vital need the presphygmic period should be lengthened. The striking disproportion between the force exhibited over the precordium and the small weak pulse of such cases suggests the thought that most of the cardiac energy is expended in the presphygmic period. In Curve 32 Ia (Tracing 15), Wave 9 shows such a systole, where a forcible cardiac contraction, as indicated by a large cardiogram, is followed by a weak short pulse, as seen in the sphygmogram. Here the aortic valves open at the point "P," and it is seen that a large part of the cardiac energy is expended in accomplishing this, and but little effect is produced in the artery. Perhaps some idea of a relative sort of the presphygmic period may be obtained by palpating the apex-beat and an artery at the same time.

#### VIII MEASUREMENT OF SYSTOLE AND DIASTOLE

It should be emphasized that in measuring the lengths of systole and of diastole on a sphygmogram in which the lowest point of the dicrotic notch of the carotid sphygmogram is used as the point where systole ends,

the presphygmic period must be added to the measurement of systole and subtracted from the measurement of diastole to give the true length of each of these phases. The length of time between the foot-point of the sphygmogram and the dicrotic notch only represents the sphygmic phase of ventricular systole. It is not correct, as we have shown, especially in cases of arrhythmia, to consider the error due to omitting the presphygmic period from the length of systole a constant. The measurement of the sphygmic period has been made from the sphygmograms in a number of cases of arrhythmia, and when the time of systole is obtained by adding the pre-sphygmic to the sphygmic time, the figures are not only much changed, but also brought nearer to a constant. This time, although it does not include the post-sphygmic phase of ventricular systole, represents more nearly and with more certainty the time of actual ventricular activity than the measurement of systole by other methods, which in the main depend on the cardiogram to determine the closure of the aortic valves and the end of systole. The importance of this correction can be seen in Table 7, where the time between the occurrence of the foot-point of the sphygmogram and of the dicrotic notch are given and the corrected time after the corresponding presphygmic time is added. The numbers are taken from Tracing 10 (31 Ic).

TABLE 7.—SYSTOLIC TIME OF SPHYGMOMGRAM AND CORRECTED SYSTOLIC TIME \*

No. of Wave	Systolic Time of Sphygmogram	True Systolic Time P P Has Been Added
1	0 231	0 275
2	0 190	0 298
3	0 260	0 309
4	0 170	0 269
5	0 290	0 322
6	0 257	
7	0 276	0 328
8	0 263	0 297
9	0 151	0 253
10	0 250	0 303
11	0 155	0 260
12	0 224	0 258

\* It is seen that while the whole length of systole may vary a little, its chief component parts, namely, the presphygmic and sphygmic periods, may change their relation to one another strikingly.

#### IX EFFECT OF VARIATIONS ON THE VENOUS PULSE

The venous pulse may be affected by variations in the length of the presphygmic time. In spite of the recent discussions of the formation of

TABLE 8—PART 1

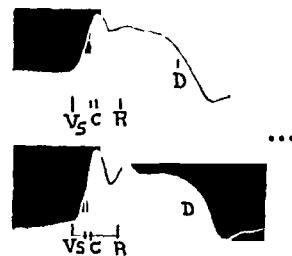
Length of P P  
in Seconds

No. of Case

Cardiograms

0.032—(0.113)

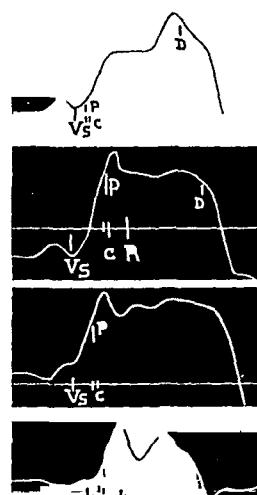
16



See also Fig 11

0.033—(0.088)

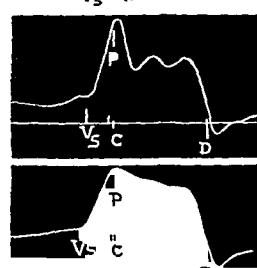
8



See also Fig 6

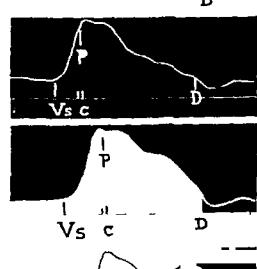
0.036

1



0.064—(0.082)

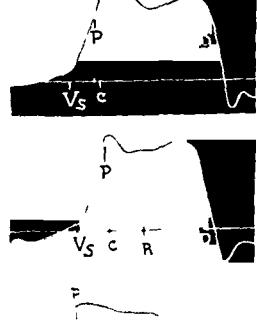
10



See also Fig 9

0.064—(0.111)

20



See also Fig 10

0.066

3



0.066

14



0.070

2



0.070

21

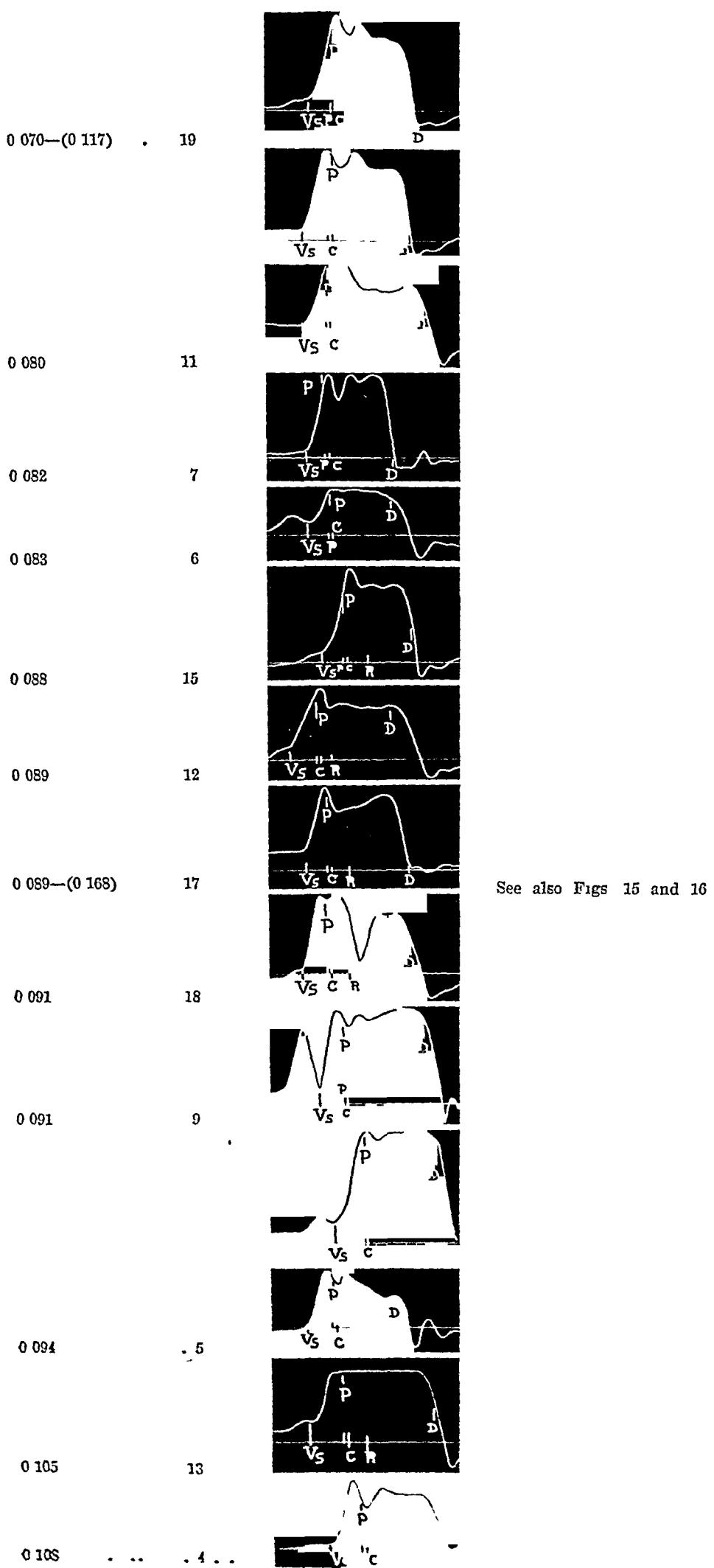
D

See also Fig 5

TABLE 8—PART 2

Length of P-P  
in Seconds    No. of Case

## Cardiograms



the C wave in the venous pulse, unity of opinion on this question does not exist. At least, in many tracings from the veins of the neck the two elements, the wave traveling up the vein from the ventricle, and the impulse derived from impact of the pulse of the carotid artery, join to form the C wave in the venous tracing. If there is a delay in the arterial wave due to a lengthened presphygmic time, this element will in all probability reach the point from which the tracing is taken later than does the C wave that travels upward through the vein. These two elements of wave production which usually move together will thus be plainly separated. This point has been discussed by Hering, and we wish here only to suggest that the prolonged presphygmic period of weak (extra) systoles may be the cause of the phenomenon of the separation of the so-called K and C waves, as Hering terms them, and account for the splitting of the C wave as observed by Hirschfelder, Bard and others.

#### X POSITION ON THE CARDIOGRAM OF THE POINT WHERE THE AORTIC VALVES OPEN AND CLOSE

The position on the cardiogram of the point where the aortic valves open has caused much discussion, and has been intimately associated with the study of the presphygmic period. In discussing this question we shall call that point on the cardiograms where the aortic valves open, that is where the presphygmic period ends, the "P" point.

Special importance was given to the question of the position of the "P" point on the cardiogram by Martius, who said that the crest of the cardiogram that is the top of the ascending limb, represented the point of opening of the aortic valves. He measured, therefore, the length of the presphygmic time by measuring the time occupied by the ascending limb of the cardiogram. Von Ziemssen and von Maximowitch accepted this idea, while Hilbert, Schmidt and others denied it. Practically all observers who mention the position of the "P" point on the cardiogram believe that it is not constant. Thus Einthoven and Geluk show that the first heart tone as recorded over the base of the heart occurs at a point about one-third up the ascending limb of the cardiogram. Diagrams of Luciani and of Buller (quoted by Nicolai) showing the relation between the intraventricular and intra-aortic pressures indicate that the former overcomes the latter about two-thirds of the way up the ascending limb. The P point was placed by Erlanger on his cardiograms from the exposed heart well after the crest of the cardiogram, near the bottom of the sharp first descending limb, at or near a point where a slight notch is seen.

The point of opening of the aortic valves has been determined on one or more typical cardiograms from each of our cases which are arranged in

Table 8 The distance of the point of termination of the presphygmic period from the foot of the cardiogram was calculated from the time of its duration, and the point P marks where the end of the period falls

In the cardiograms there is also marked the point D. The position of this point has been determined in the following way. The distance between the foot-point and the deepest point of the dicrotic notch has been measured on the carotid sphygmogram of the same heart-beat that produced the cardiogram. This distance was measured on the cardiogram from the P point. If, therefore, the P point represents the opening of the aortic valves, that is, the beginning of the sphygmic period, the point D will represent the point where the sphygmic period ends, that is, the point of closure of the aortic valves, provided that that phase of the sphygmogram between the foot-point and the dicrotic notch represents the sphygmic phase of the cardiac cycle.

These methods of determining the points on the cardiogram of the opening and closing of the aortic valves may lack mathematical correctness, but they seem to be more nearly correct than any other methods applicable to man. Besides the position of the P and D points, Table 8 shows the lack of relation between the shape of the cardiogram and the length of the presphygmic periods.

It is seen that the position of the P point on the cardiogram is not constant. There is, however, a fairly definite relation between its position and the length of the presphygmic time. This relation shows that the aortic valves open at points which come relatively earlier on the cardiograms with short presphygmic periods than they do when the presphygmic periods are long. The lateness of the P point that occurs with a long presphygmic time is seen in Curve 32 Ia, Wave 9 (Tracing 15). Here it is well shown what a large part of the cardiogram may represent the presphygmic period, and by observing the other cardiograms of this curve (Tracing 14) where the period varied greatly, it will be noticed that the change of point of opening of the aortic valves has no effect on the shape of the cardiogram. We cannot expect cardiograms taken through the normal chest wall to give any indication of the point of opening of the aortic valves, when in the tracings of Erlanger from the exposed heart the cardiogram shows but a slight indefinite notch at this point.

Although the position of the P point varies in the cardiogram with variations in the presphygmic period, its position in the five cases that we consider normal is quite constant. In all of them the P point falls near the top or three-quarters of the way up the ascending limb of the cardiogram, and this at least indicates that here is the point in a cardiogram from a normal individual where the aortic valves open. In but two cases

that we have considered abnormal, Nos 7 and 14, which lie just above and just below, in Table 8, the group of normal cases, do the P points fall in this part of the cardiogram.

The position of the D point is seen to vary and to fall at different points on the final descending limb of the cardiogram. This variation may be due to recording the end of systole by the cardiogram in an inconstant manner, or it may be that the sphygmograms from which the presphygmic periods have been calculated contain errors that have not been constant. We believe that not a great deal of dependence can be put in the last part of a cardiogram as forming a record of the true movements of the heart, and that the position of the D point on the cardiogram has no significance. There seems to be no indication on the cardiograms that we have obtained of the point at which the aortic valves close.

#### XI RELATION OF FORM OF CARDIOGRAM TO LENGTH OF PRESPHYGMIC PERIOD

Table 8 shows also that there is no relation between the length of the presphygmic period and the shape of the cardiogram, especially in regard to the degree of sharpness or suddenness of its ascending limb. In the cardiograms that we have made there is no indication of the point at which the aortic valves open, and the form of the cardiogram affords no evidence as to the duration of the presphygmic period. In this regard our work confirms the belief of those who say that nothing in regard to the heart's action can be told from the cardiogram.

The relation between the so-called I wave in the cardiogram and the point of opening of the aortic valves has already been alluded to. This wave was considered by Piersol, working in Wenckebach's laboratory, as definitely related to and representing the ventricular presphygmic period, a conception in which we shared at the outset of our work. The I wave is well seen in some of the tracings from four of our cases. In one case the P point is practically synchronous with the end of the I wave, in the second it is 0.018 second later, and in the third it is well removed. In the fourth case, No. 8, in which marked variations in the presphygmic period are seen, the I wave when present is practically constant in length, and although with a short period the P point is synchronous with the end of the I wave, with a long period this point falls high up on the ascending limb of the cardiogram, and is far removed from the end of the I wave. These findings, together with the fact that the P point can fall much later in the cardiogram than the top of the ascending limb, make it evident that the I wave bears no relation to the presphygmic period of ventricular systole.

## XII CONCLUSIONS

Although we feel that our work has many deficiencies, and must be completed by further investigations, certain conclusions are justified. It is our hope to continue the work in order especially to obtain more certainty in regard to the normal duration of the presphygmic period, to investigate more fully those conditions that lead to a shortening of the presphygmic time, to determine its prognostic value and to obtain a better knowledge of those factors in cardiac arrhythmia underlying the fact that in some cases of arrhythmia the presphygmic period varies while in others it remains constant. We expect also to attempt to control the results of this work as far as possible by experiments on animals.

1. The normal duration of the presphygmic period of the ventricular systole of the heart is from 0.07 to 0.085 second.

2. This time cannot be measured with mathematical exactness, but by carefully guarding against a number of technical difficulties its measurement approaches very near to such exactness.

3. Under various pathological conditions the duration of the presphygmic period may vary markedly, under some conditions being below and under other conditions being above the normal limits.

4. Changes in the circulatory apparatus, of which arteriosclerosis is a part, seemed to have a marked tendency to shorten the duration of the presphygmic period in three such cases studied.

5. It is probable that the amount of lengthening of the presphygmic period beyond the normal limits is an index of diminished capability of the heart, whether it is caused by valvular, muscular or arterial disease or a combination of lesions.

6. Valvular heart disease as such, when it is uncomplicated by muscular weakness or some disturbance in the accommodating or compensating functions of the heart, does not necessarily cause prolongation of the presphygmic period. Mitral insufficiency may prolong the period, while aortic insufficiency may shorten it.

7. Changes in speed of pulse-wave transmission bear no apparent relation to changes in the presphygmic time.

8. A case of neurotic instability of the circulatory apparatus without arrhythmia has shown different presphygmic times on various occasions, although variations in the presphygmic periods of consecutive systoles have not been found. It is thought that this variation represents possibly a manifestation of the varying nervous excitability or instability of the heart, just as the readily varying pulse frequency seems to do. No definite relation between pulse frequency and the duration of the presphygmic period was discovered.

9 In certain forms of arrhythmia there was marked irregularity in the presphygmic time of various consecutive systoles. These variations depended largely on and bear a fairly definite relation to the duration of the preceding diastole. The apparent force of the preceding systole had also a definite effect on the duration of the presphygmic period of the following systole. In these cases of arrhythmia an apparently weak systole followed by a long diastole formed the best conditions for the production of the shortest possible presphygmic period in the following systole in each case, while a strong systole followed by a short diastole produced the longest presphygmic time.

10 Other cases of arrhythmia apparently depending on nervous control of the heart or on a depression in stimulability of the ventricle (bathmotrophic disturbance) showed practically constant presphygmic time. Where variations occurred in these cases there was no relation between them and the variations in the length of diastole.

11 The factors producing the differences in these two forms of arrhythmia are difficult to determine, but in the first group of cases the accommodating power of the heart seemed damaged or lost, while in the second group it was well preserved.

12 A so-called frustrated systole that fails to open the aortic valves represents the presphygmic phase of a ventricular contraction that produces no sphygmic phase.

13 In cases of cardiac disease, in which there is a striking disproportion between the force of the heart exhibited over the precordium and the small weak pulse at the wrist, it is probable that a large part of the cardiac energy is expended in the presphygmic period.

14 The length of duration of ventricular systole can be measured by estimating the time between the foot-point and the dicrotic notch in the carotid sphygmogram, and by adding to it the presphygmic time for this particular systole. By this method a result is obtained which probably represents more nearly than the results from other methods the time of systolic activity of the ventricles.

15 There is no indication in our cardiograms of the point at which the aortic valves open or close, nor do the forms of the cardiograms depend in any way on the duration of the presphygmic period of the ventricular systole.

It is with much pleasure that we express our appreciation of the interest that Professor Muller has taken in our work, and our thanks are due him for being able to avail ourselves of the splendid opportunities that his clinic affords. We wish to thank Dr. Ernst Edens for much advice and helpful suggestions. Our work was greatly aided by the use of

his large material, especially his venous and esophageal tracings. Our gratitude is also due to all the assistants of the second medical clinic in Munich for many courtesies and aid in studying the material in their various wards.

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## BLOOD-SPOTS A MEDICOLEGAL STUDY

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In the medicolegal study of cases of violent death the location and gross appearance of blood-stains at times become important factors. Their significance is, however, referred to but very briefly in works on medical jurisprudence, and the part which blood-drops falling vertically may play in solving the riddles which these cases present has been hardly noticed. A search through the available English, German and French works on the subject shows practically nothing regarding these latter blood-spots.

Withaus and Becker's last edition<sup>1</sup> says "Blood dropped perpendicularly on a hard smooth surface begins to spatter when the height reaches 3 or 4 inches, but may not spatter from a height of 2 or 3 feet. Dropped from a few inches on glass, the drop is compact with smooth edge, from a few feet, the drop is flatter, the edges may be moderately indented, and minute outlying drops may be present."

Babcock<sup>2</sup> says "Drops of blood from a height of 1 or 2 feet are larger than those falling only a few inches. In the first case the circumferences of the spots are deeply indented, but in the second they show a perfectly regular outline." He gives two illustrations of such drops; one shows them almost perfectly round and smooth, the other has short spicules arranged nearly as regularly as the spokes to a wheel.

The statements made by other authors are no more complete than those quoted. The failure to discuss these spots more fully is doubtless due to the infrequency with which they become of importance. That they must occasionally be studied with reference to the height from which they fall was evident in a case investigated by one of us in which the question came up whether certain blood-spots found on stains might have been

<sup>1</sup> From the Pathological Laboratory of the Yale Medical School

<sup>2</sup> We are indebted to Dr H S Arnold instructor in pathology in the Yale Medical School for the numerous photographs which he has taken of our specimens.

1 Withaus and Becker Medical Jurisprudence and Toxicology, New York 1909 in 811 William Wood & Co

2 Babcock In Hamilton's System of Legal Medicine New York, 1900 p 155, E B Tient & Co

made by blood dropping from the height of the ear of a man of medium stature when standing, or whether their size and shape were inconsistent with the blood having fallen from so great a height. The study of these spots was one of the factors in reaching a decision between murder and suicide.

These experiments were undertaken for the purpose of determining what inference can be drawn regarding the height from which blood dropped from the size and shape of the dried blood-spot, or, stated in another way, what factors, aside from the height from which the blood fell, are of importance in determining the size and shape of the resulting dried blood-spot when blood drops vertically. All of the experiments were made by allowing the blood to fall vertically on the surfaces tested. Rabbit's blood was employed throughout. The animal was first given a sufficient dose of chloral to put it to sleep in fifteen to thirty minutes and so to render it insensible to pain. When insensible, it was suspended by the hind legs and blood-drops obtained by clipping off a bit from the tip of the ear. In addition, as opportunity presented, we have noted the appearance of drops of human blood which have fallen from a known height. The shape of the latter agree with the results of our experiments with rabbit's blood.

Different varieties of wood were used in most of the tests, but in addition glass and surfaces covered with paper were employed. The kinds of wood were white wood, planed, white wood, planed and sandpapered, hard pine, planed, hard pine, planed and oiled, hard pine, rough, hard pine, rough and oiled, oak, planed and varnished, soft pine, planed and enameled, soft pine, planed. Paper wall-paper, pasted on smooth board, wall-paper, face down, pasted on smooth board. Glass clean glass, glass, covered with a thick layer of dust. Other substances were also tested in other series of experiments, but the results obtained corresponded to the series here quoted. In this series all of the blood-drops were on objects of about the same size, 12 by 10 to 11 inches and were so photographed as to give the same relative size in each case.

The surfaces on which the blood drops fell evidently differed very much in smoothness. Some were smooth and entirely non-absorbent, others smooth and slightly absorbent, like the white wood. Some were rough and somewhat porous, as the hard pine in the condition in which it came from the saw. Others were made a little smoother and non-absorbent by oiling rough pine boards.

In the first series here described, each surface has eight blood-drops on it. One of these drops fell from each of the following heights: 2 inches, 6 inches, 1 2 3 4 5 and 6 feet. In this way a drop from any

Fig. 1—Clean glass. Spots made by blood drops falling vertically from the heights indicated. The illustrations have been uniformly reduced in size.

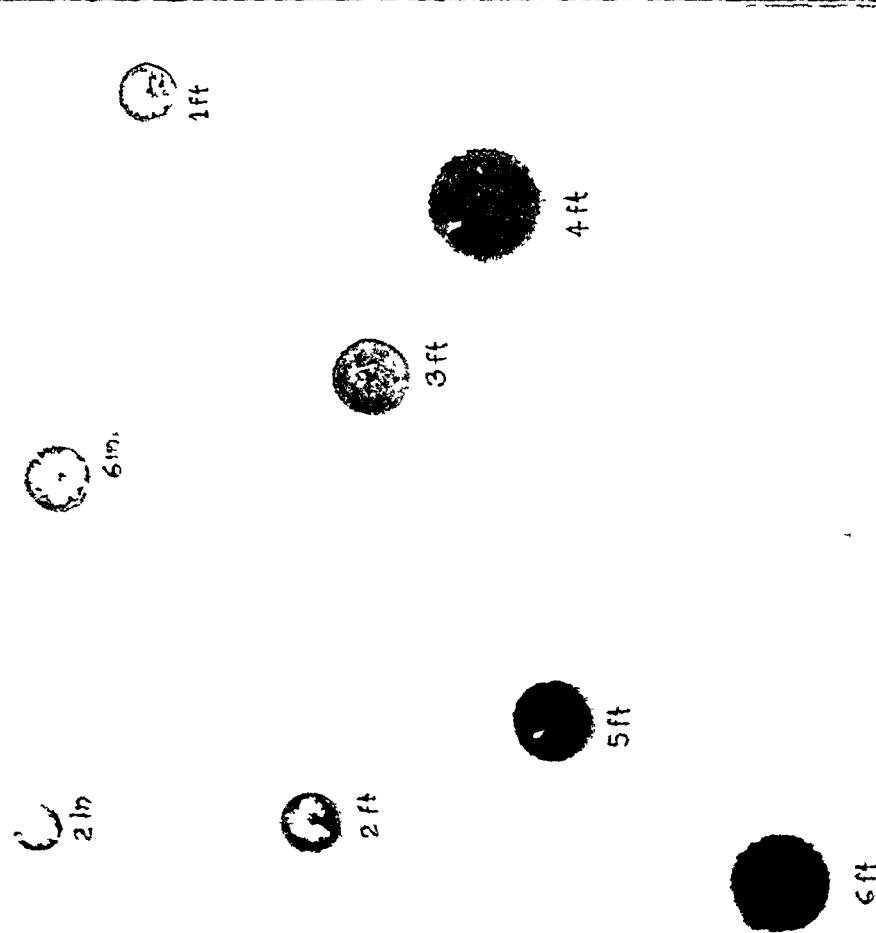
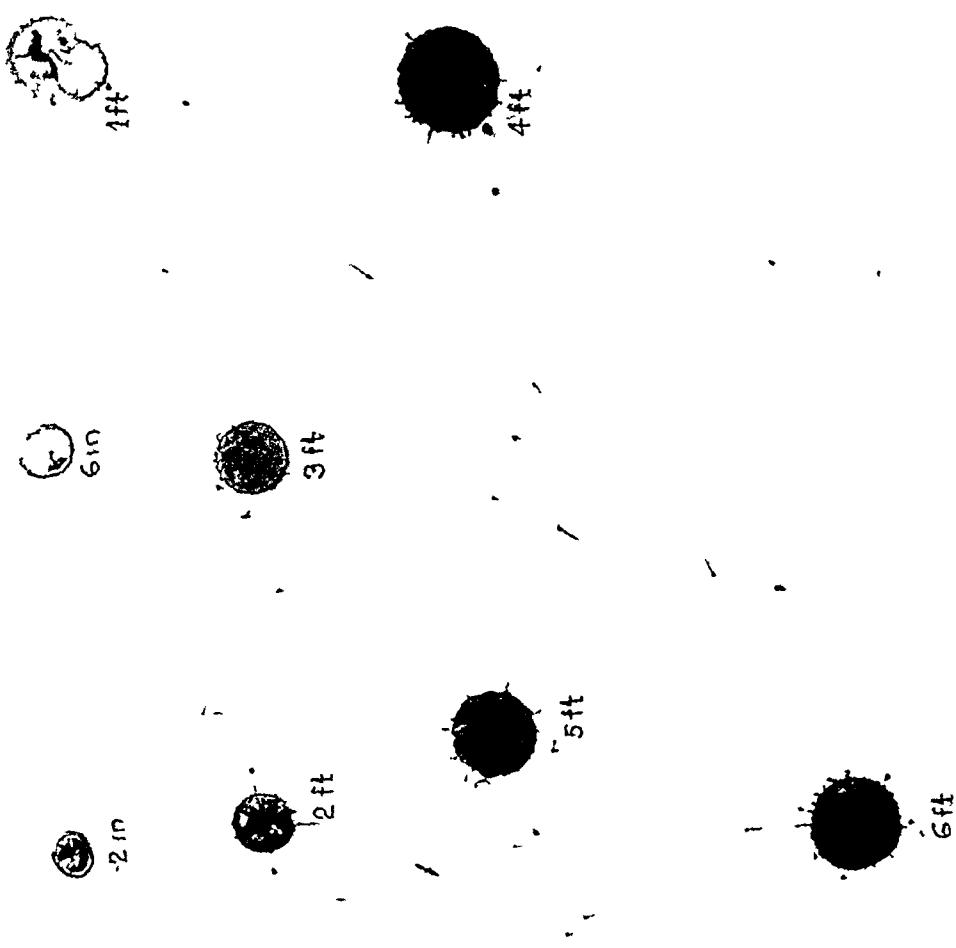


Fig. 2—Dusty glass. Spots made by blood-drops falling vertically from the height indicated



given height on one surface can be compared with a drop from the same height on a different surface. The appearance of the drops on the smoother surfaces will first be given, then those on rougher surfaces.

Clean glass is a good example of a smooth, non-absorbent surface. As seen in the accompanying illustration (Fig. 1), the drops on clean glass in general increase in size with the height. This is not uniformly so. For example, the 6-inch drop is larger than the 1-foot or 2-foot drops and the drop which fell 4 feet is much larger than any of the others. An explanation of this will be seen later. The smaller drops are almost entirely smooth on the edge. Those falling from a greater height, 4 to 6 feet, show several short, thick spicules, the number or length of these not depending entirely on the height. They are here more marked in the 4-foot drop than in the others. The smaller drops, those from 2 inches up to 2 or 3 feet form a thicker layer of blood than those from a greater height and show a tendency to crack radially and to become separated from the glass and easily dislodged. This is well shown in several of the drops in Figure 1, where considerable parts of the smaller drops have fallen from the glass. It is also noticeable that the larger drops show a breaking up into very numerous irregular areas with minute cracks between them. In general, the greater the height from which the drops fell the thinner the layer of blood. This, however, is hardly sufficient to differentiate between a 6-foot drop and one falling a somewhat less distance. None of the drops on this plate showed marked spicules and few show spatters. If the latter occur, as they do at times on clean glass they appear as small, rounded spots at a short distance from the main drop.

The contrast between blood-drops on clean glass and those made on glass thickly covered with dust is striking (Fig. 2). Here the drops up to 6 inches are still practically smooth. The size and thickness of the drops, in general, does not differ materially from those in Figure 1. Here again it is also evident that the size of the drop does not always vary as the height. It is in the formation of spicules and spatters that the chief difference between Figure 1 and Figure 2 is seen. In the latter they are present in the 1-foot drop, and are fully as marked in the 4-foot drop as in the 6-foot drop. The spicules are, in general, rather short. The spatters are, however, very numerous and have extended a considerable distance from the main drop the farthest ones being at least 6 inches from the nearest drop. The shape of the spatters here is in contrast to that in Figure 1. On clean glass as on other strictly smooth surfaces, the spatters, if present at all, are round and situated near the main drop. There are no irregularities to throw them in any particular direction. But

Fig. 4.—White wood, planed  
Spots made by blood drops falling vertically  
from the heights indicated

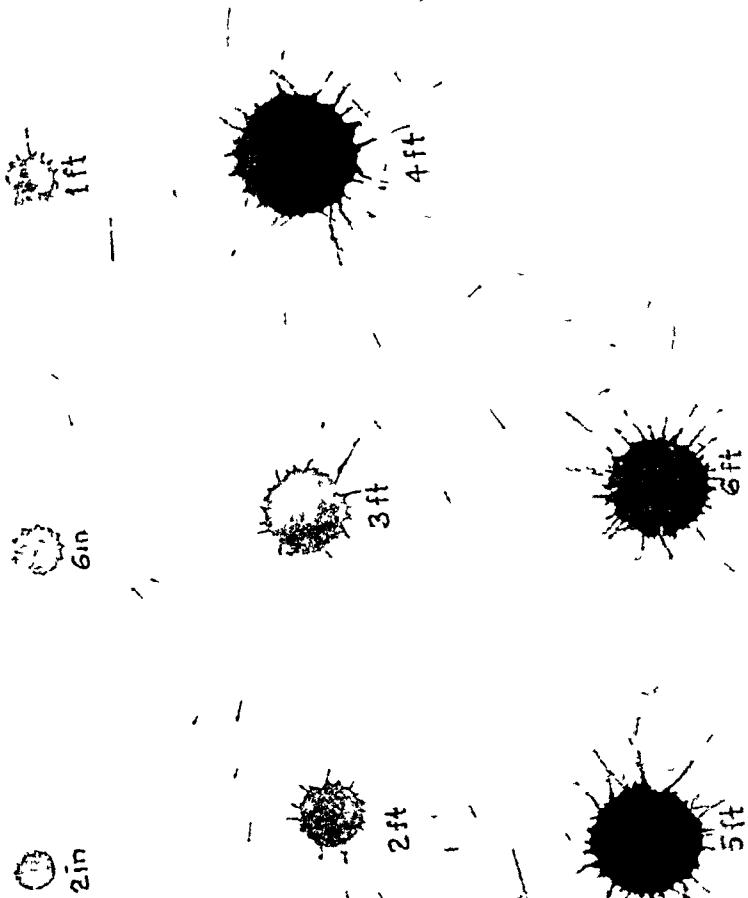
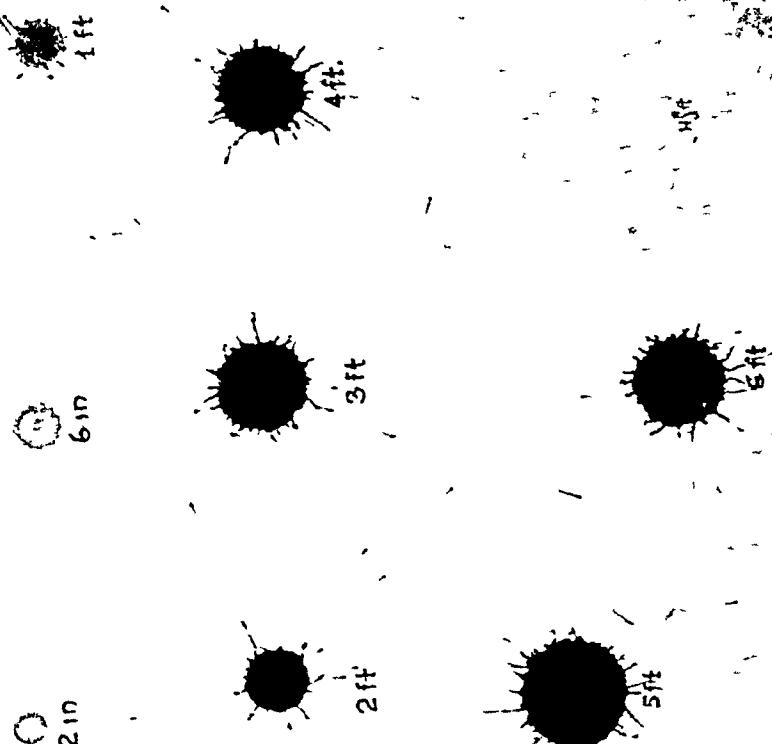


Fig. 3.—White wood, planed and sanded  
Spots made by blood drops falling vertically  
from the heights indicated



minute irregularities furnished by dust particles on glass are sufficient to cause considerable spattering and to throw a part of the blood droplets with enough force to produce elongation of some of the spatters. The same factor has given the more marked spicule formation as seen in Figure 2. The tendency for the smaller drops to separate from the glass, and for the larger ones to divide into small irregular areas, is seen here as in Figure 1. The 1-foot drop is probably more irregular than it would have been if it had not fallen on the rim of another drop. The first 1-foot drop had dried and separated from the glass, except at its outer part, and it was on the edge of this first drop that the second one fell.

Another glass plate, not shown in the illustrations, had dirt in small specks dried on it, so that it could be removed only by washing. This showed a decided exaggeration of the spicules and spatters described in Figure 2.

Soft pine, planed, covered with two coats of white enamel paint, furnished another very smooth surface. Spicule formation and spattering is hardly more marked than on clean glass. The dried blood is more adherent than it is on glass and no tendency to separate from the painted surface is evident. There is the same separation into small pieces with minute cracks between them which was seen in the larger drops on glass. The interesting thing about this specimen is the very small size of the 6-foot drop, which measures 19 mm. It is smaller than that from 3 feet (21 mm.). It is scarcely more irregular on the surface than the 3-foot drop, showing no spattering. The layer of blood in the 6-foot drop is a little thinner than in either of the other drops.

A surface very similar to the last was obtained by pasting white enameled paper, such as is used for making sphygmographic tracings, on a planed board. The spots correspond closely with those on the white enamel paint as regards spatters and spicules.

The spots on a smooth, varnished oak board gave even less spicule formation and practically no spattering. The slight irregularities seen at the periphery of the drop are blunter than those on clean glass or the other smooth surfaces mentioned.

White wood, planed and sandpapered (Fig. 3), gave a very smooth surface. The contrast between the drops on it and those just described is, however, striking. This is not noticeable in the 2-inch spot, but already in the 6-inch spot we find blunt, short spicules. From one foot up the spicule formation and spattering become very noticeable. The 6-foot drop shows these but little, if at all, more than do the 3-foot and 4-foot drops. The size of the drops gradually increases with the height from which the blood fell, but, as in previous illustrations, this is not always

Fig. 5.—Hard pine, planed and oiled  
fully from the heights indicated

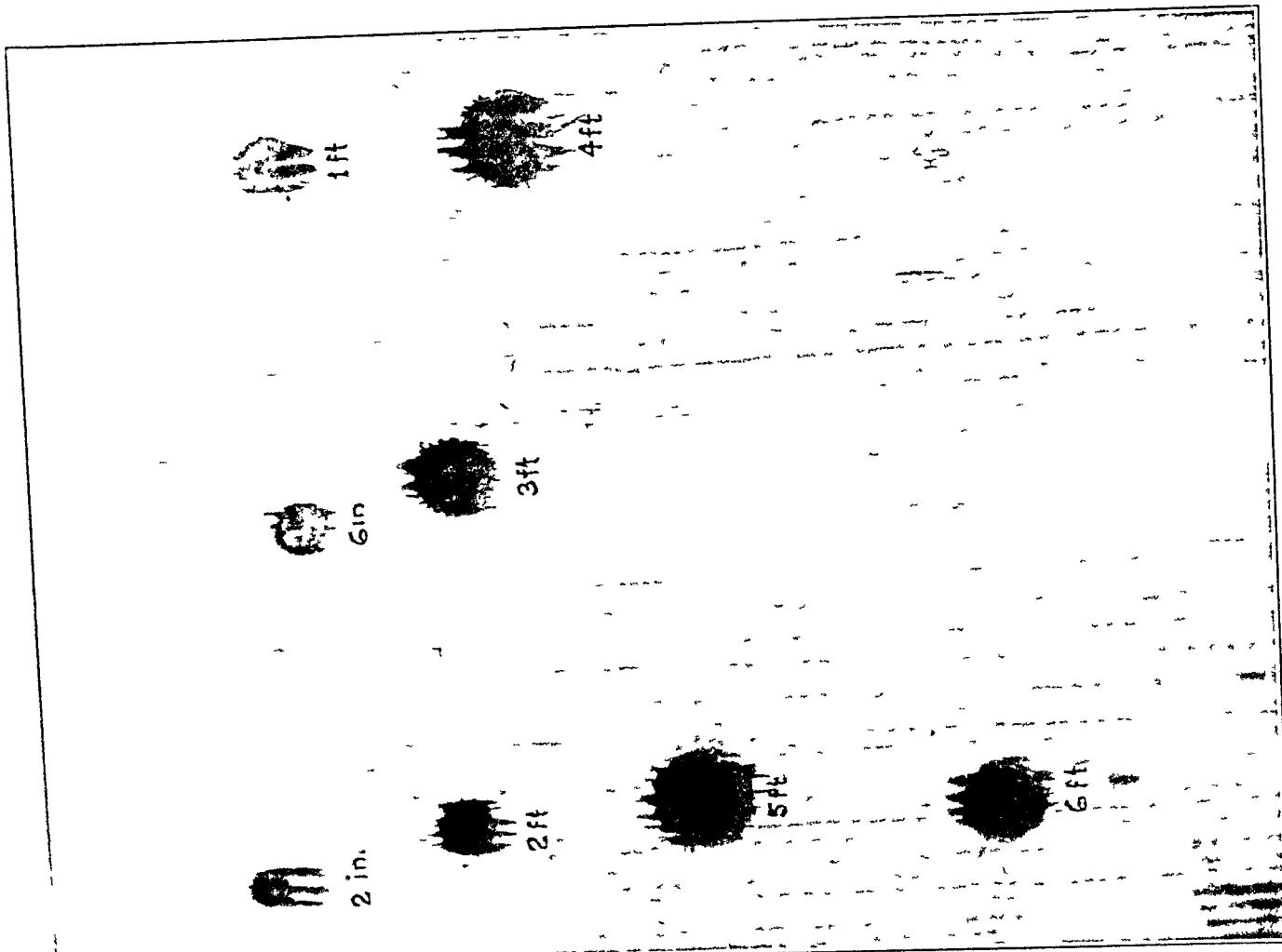
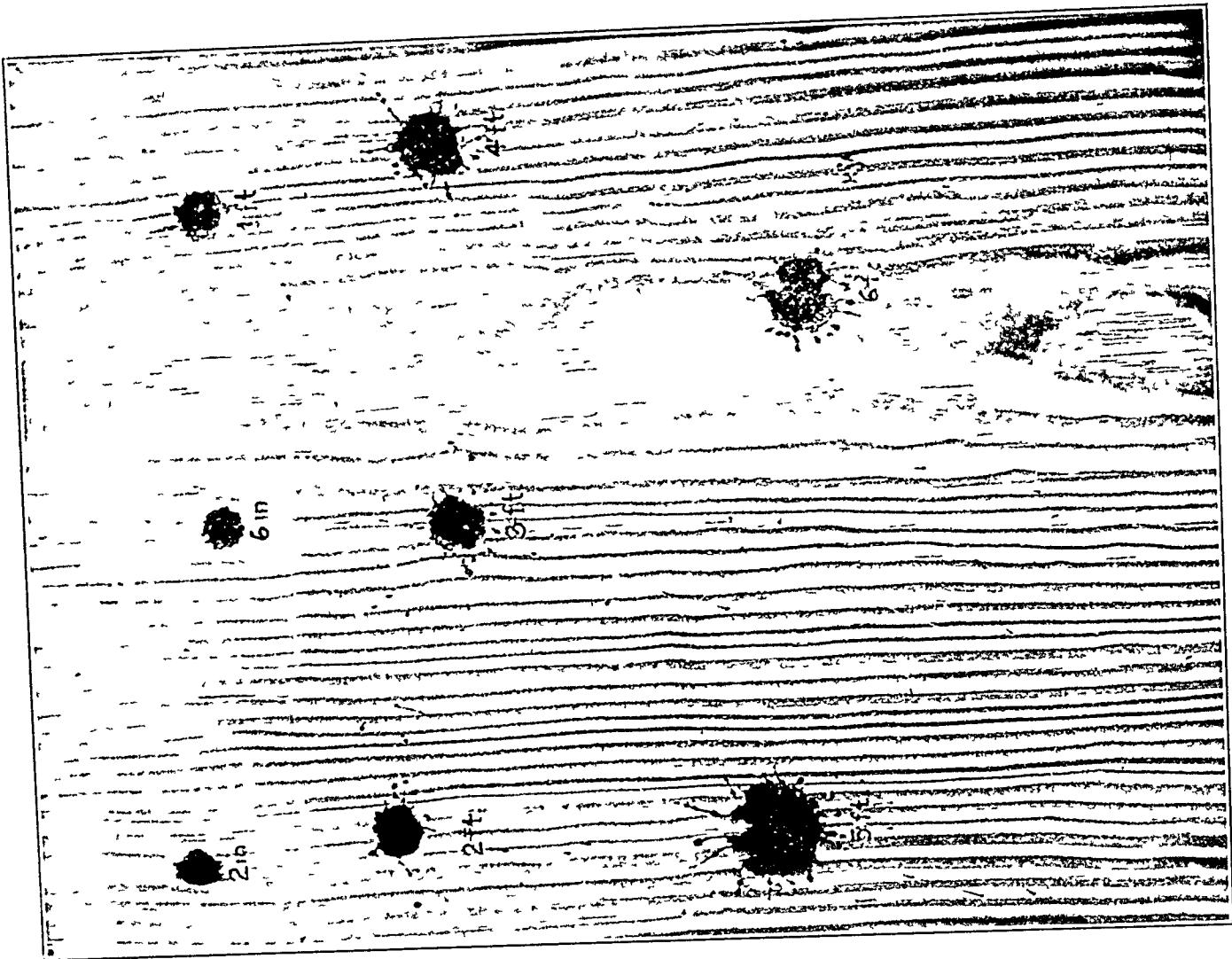


Fig. 6.—Hard pine, planed and oiled  
vertically from the heights indicated



the case. Here, again, the 6-foot drop is not larger than the 3-foot drop and is considerably smaller than the 5-foot one. The last shows a slightly thicker layer of blood than the first, and the spicules are perhaps somewhat thicker. This is, however, not marked enough to certainly differentiate the two. The spattering has extended several inches from the drops, going as far as the edges of the board. Nearly all of the spatters here have been thrown with such force as to make the resulting spots elongated.

The board of white wood, planed (Fig. 4), is similar to the last except that it is slightly rougher, not having been sandpapered. Comparison of the drops shown in Figures 3 and 4 shows at once the effect of this slight roughness. The size of the drops approximates that of the last plate, but many of the spicules and spatters are longer, indicating that they were thrown with more force. Here, again, the great difficulty, if not impossibility, of telling the difference between the 4-foot, 5-foot and 6-foot drops is apparent.

The board of hard pine, planed (Fig. 5), appeared to be about as smooth as the last one. Yet a comparison of Figures 4 and 5 shows a great difference in the appearance of blood-drops falling from the same height on the two surfaces. As seen in Figure 5, there is but a moderate amount of real spicule formation and very little spattering from any of the drops. The blood has soaked into the wood much more than in the case of the white wood, and so shows an elongation of the drops along the grain of the wood. There is little to differentiate the drops between 2 feet and 6 feet, except the size, and this by no means increases regularly with the height.

The hard pine, planed and oiled (Fig. 6), is similar to the last, except that it has been oiled. The two pieces came from the same board. The marked difference between the blood-spots on the two boards is seen at a glance from the illustrations. The main part of the spot is smaller on the oiled board than is the corresponding drop on the one which is not oiled. But the striking difference is in the spicules, and more particularly in the spatters. This is shown in all of the drops from 2 feet up. It is most marked in the 4-foot and 5-foot drops. Instead of extending out as marginal spicules connected with the main drop, as seen in the drops on planed white wood (Fig. 4), many of the irregular extensions here are not connected with the main spot at all. They appear as marginal spatters instead of spicules. This may have been caused by the retraction of the main drop before drying because of the oiled surface on which it fell, thus leaving the spicules separated from the drop.

Fig. 7.—Hard pine rough  
Spots made by blood drops falling  
from the heights indicated

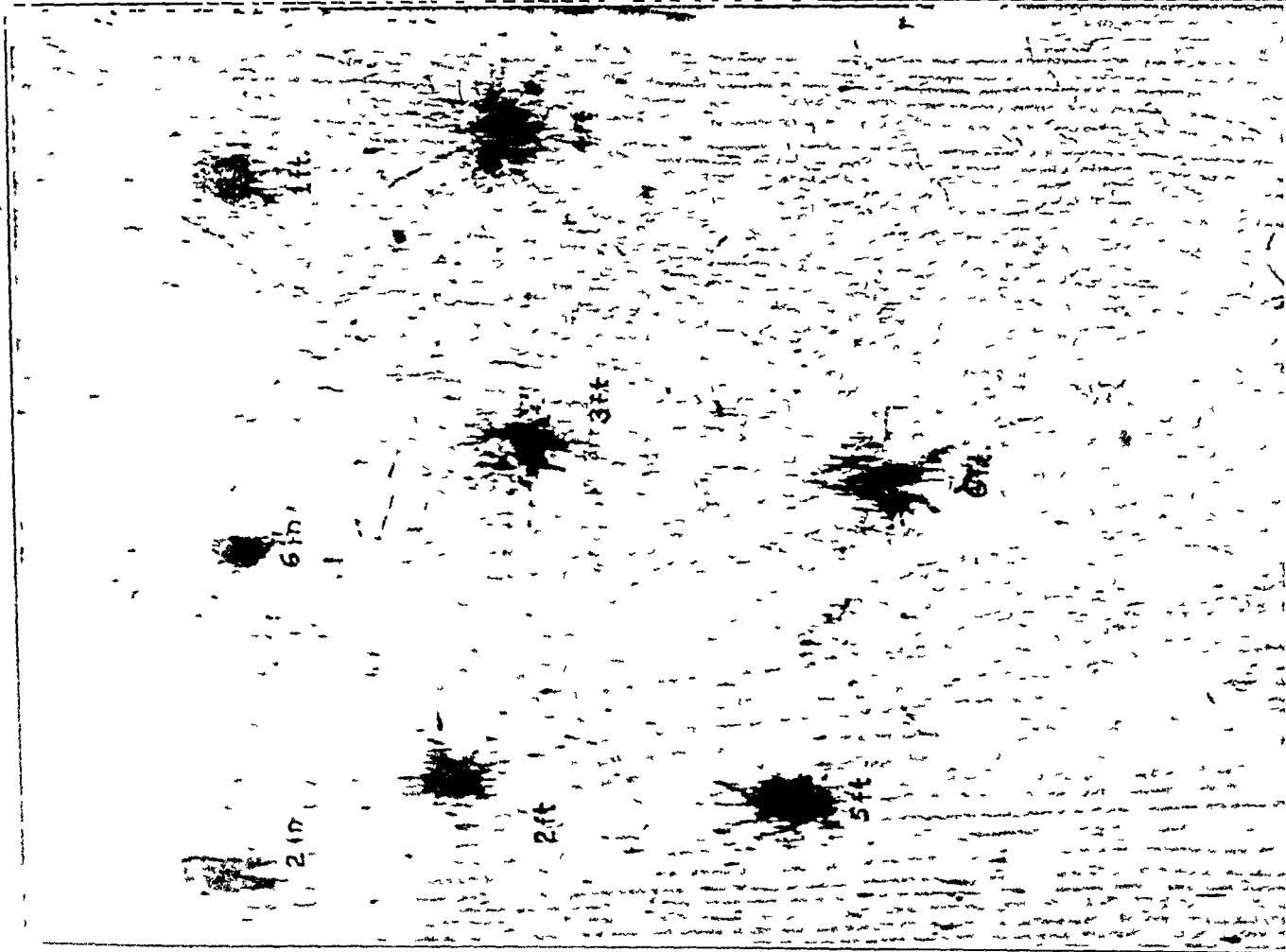
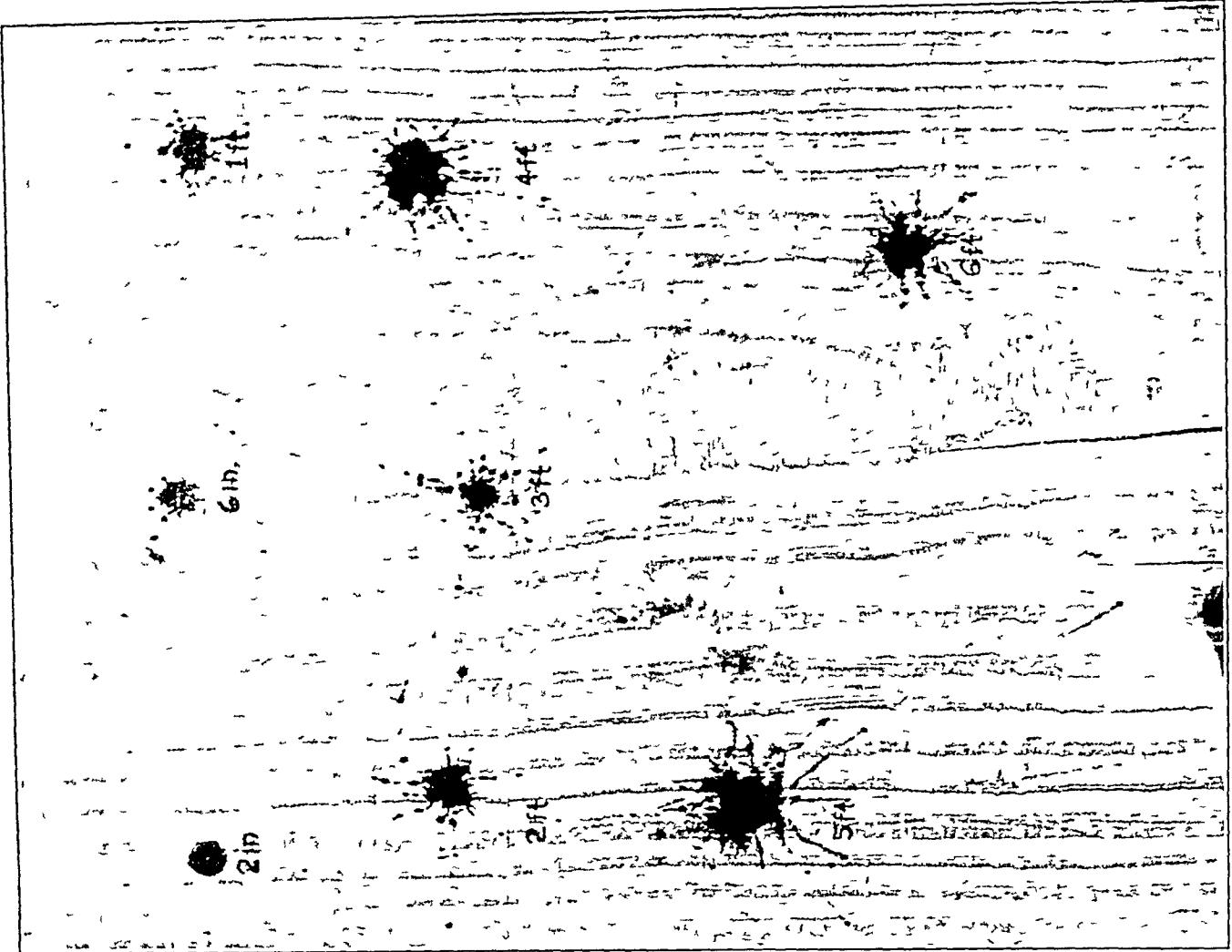


Fig. 8.—Hard pine rough and oiled  
Spots made by blood drops falling  
vertically from the heights indicated



The rough, hard pine (Fig 7) is a surface as it came from the saw, except that it was slightly smoothed by rubbing one board over another. Here, again, the appearance of the drops is well shown in the illustration. Spattering and spicule formation become evident in the 1-foot drop. In this case it is most marked in the 4-foot drop. As was seen in the planed, hard pine board, the blood here was absorbed before drying, thus somewhat increasing the size of the spot.

In the rough, hard pine, oiled (Fig 8), again, the effect of oil on the surface is well seen. The chief differences between this board and the last one are the greater distinctness of the drops, due to non-absorption of the blood; the very marked spicule formation which begins in the 6-inch drop and is very marked in the 5-foot drop, the amount of spattering and the evident force with which these spatters were thrown, as shown by their elongation. As in the case of the hard pine, planed and oiled, many of the spicules here are not connected with the main spot, probably owing to the retraction of the blood-drop before drying. The minute, white specks on the smaller drops, as seen in the illustration, are not due to the dislodgment of bits of the dried blood, but are apparently caused by the reflection of light due to the irregularity of the surface.

The specimen of wall-paper (Fig 9) was made by pasting wall-paper with a fairly smooth surface on a planed board. Spicule formation is present in all of the drops except the 2-inch one. It becomes marked with the formation of spatters at 1 foot, and from 2 feet up to 6 feet these are very marked. It is to be noted how very much some of the drops are broken up. This is seen particularly in the 5-foot drop, where a considerable part of the spot is made up of irregular spicules and marginal spatters. Spatters have been thrown to a considerable distance, and with force as is evident from the shape.

Wall-paper, pasted face down on a planed board, gives a surface slightly rougher than the last. Spicule formation is quite marked even in the 6-inch drop. In general, the spicule formation is more marked than in the last specimen and spatters have extended in nearly all directions from each drop, from the 6-inch one up to those from a greater height.

Very little comment is necessary regarding the effect of the kind of surface on which blood-drops fall, as demonstrated by this series. A comparison of the 4-foot drops, for instance, on the different surfaces as shown in the illustrations, makes the importance of the smoothness or roughness of the surface very evident. In fact, this is the important factor in the case of all drops falling from 1 foot to 6 feet. The height is a secondary matter.

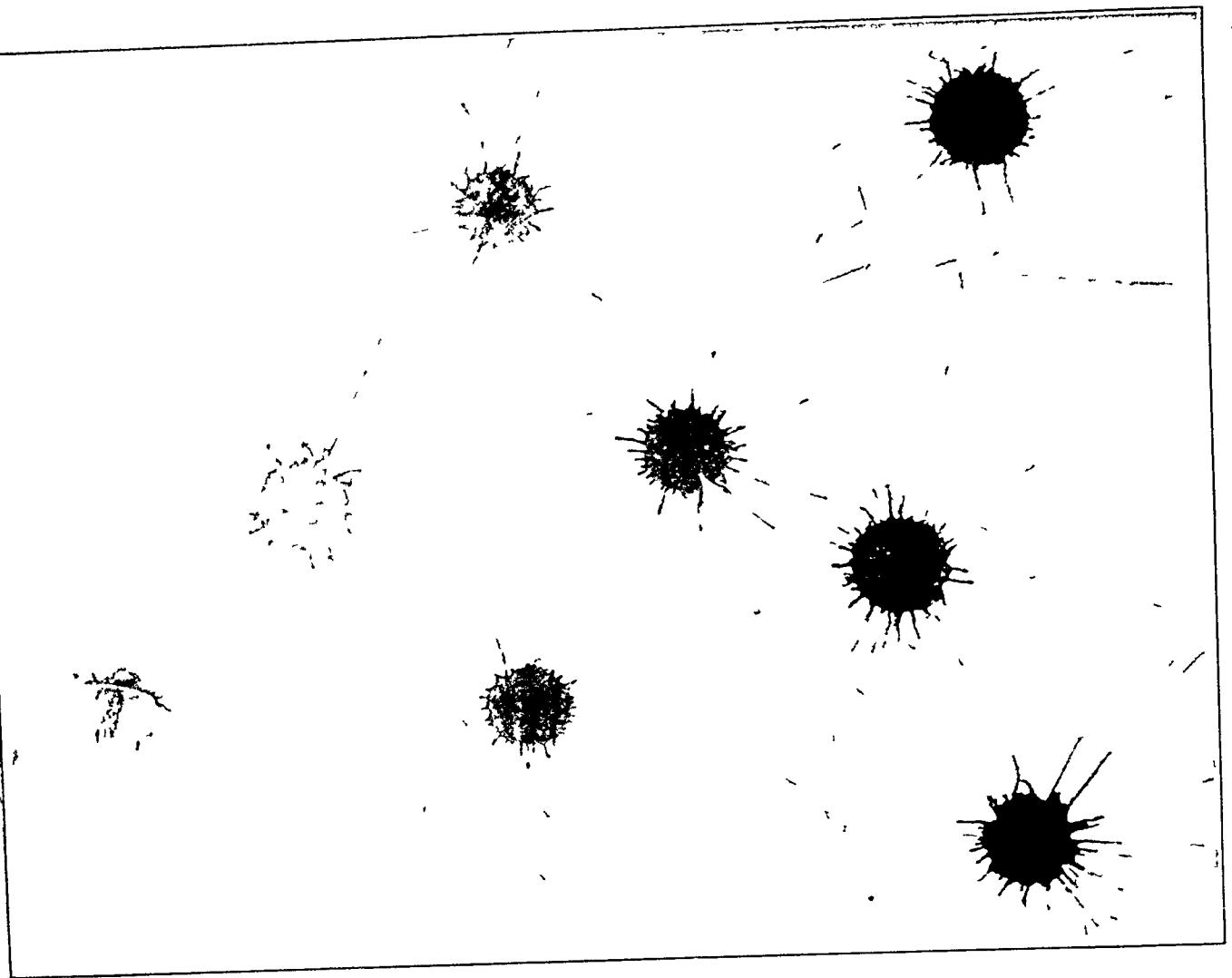


Fig. 10.—Planned white wood. Spots made by blood drops falling vertically 5 feet

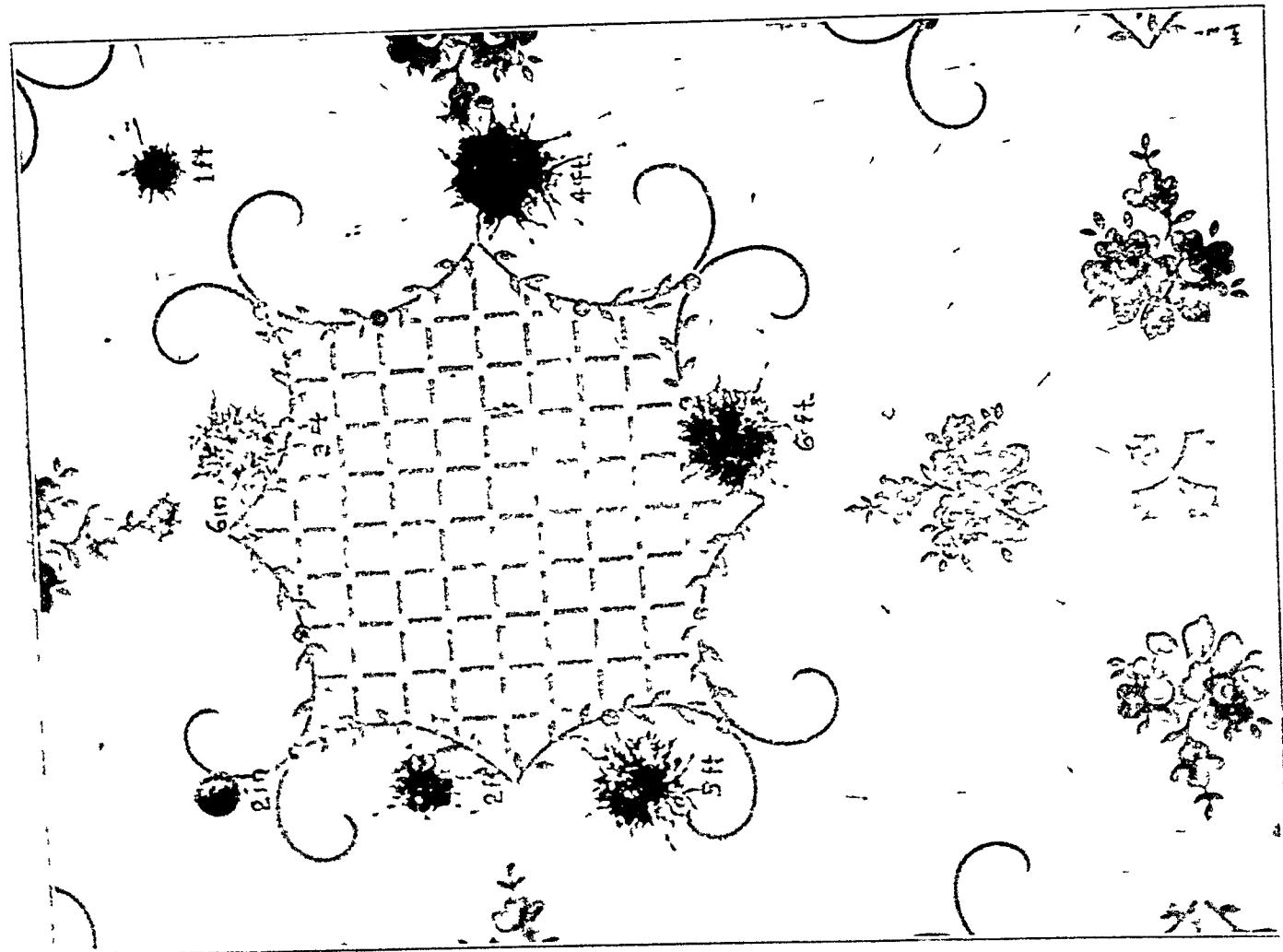


Fig. 9.—Wall paper, pasted on to smooth board. Spots made by blood drops falling vertically from the heights indicated

Attention has been called to the fact that frequently a drop falling a less distance has made a larger blood-spot than one falling a greater distance on the same surface. The obvious explanation for this is that some drops were larger than others when they fell. It was noticeable as the blood dropped from the rabbit's ear that the drops varied in size. This in part, depended on whether the ear had been so cut that the blood dropped from a very acute angle or from a somewhat blunter one, also on the rapidity with which the blood came from the ear. When this was very slow, so that the blood had time to become slightly more viscid before falling, the drop was naturally larger than when the bleeding was more rapid. This difference in the size of the drops is a disturbing factor in attempting to determine the height from which the blood fell by the size of the blood-spot.

The next set of tests was made to find how great the similarity is between drops which have fallen from the same height on the same kind of a surface. The different surfaces tried for this were white wood, planed, white wood, sandpapered, soft pine, planed, hard pine, planed and oiled. The height varied from 2 feet to 6 feet. The single illustration shown of this series (Fig. 10) gives a fair idea of the results. This shows drops all falling from the height of 5 feet on to planed, white wood. As seen in the illustration, the difference in size is considerable, the spots exclusive of spicules measuring from 18 mm to 23 mm. In other tests, considerable more variation in size was found than is evident here. Considerable variation in the degree of spicule formation and spattering is also evident in the spots shown in Figure 10. This series merely confirms what we have been led to expect from the first series, that drops falling from a given height on the same surface may vary considerably in the appearance of the resulting blood-spots.

Thus far it has been found impossible to determine from the appearance of individual drops whether they fell 3, 4, 5 or 6 feet. The next attempt was to study more carefully the spatters, as well as the spicules, from individual spots to see if any evidence of the effect of height could be obtained in this way. For this purpose a single drop of blood was allowed to fall on a surface and the degree of spattering, as well as the appearance of the spatters, particularly as regards elongation, was noted. These were studied under slight magnification, as well as with the unaided eye. Also the relative length and thickness of the spicules were more carefully noted than heretofore. Over thirty preparations of this kind were made, the surfaces being of the same character as already indicated. Drops of blood were allowed to fall from 2 feet to 6 feet. Only a single drop fell on any one board. It seemed probable that the shape of the spatters

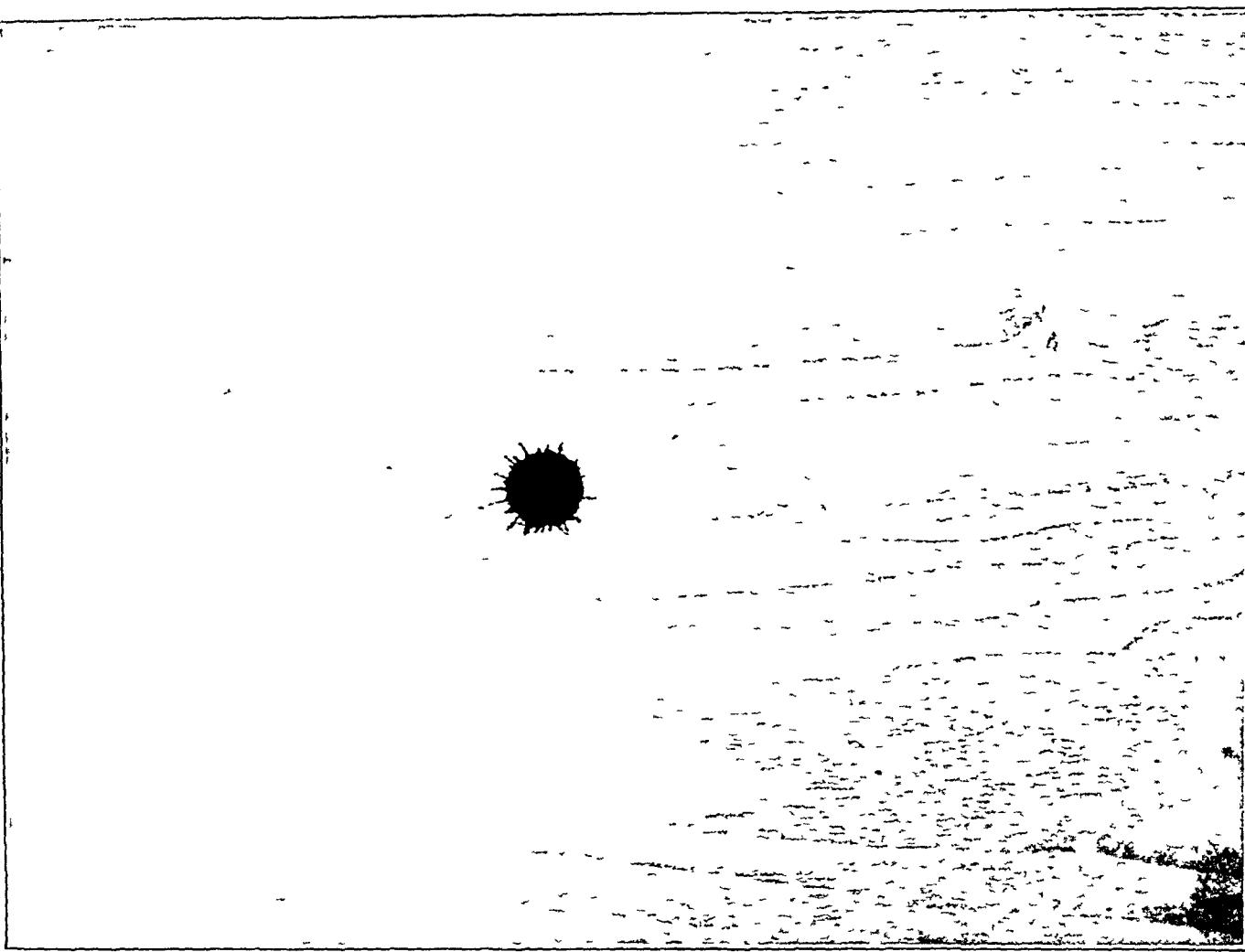


Fig. 12.—White wood, planed and sandpapered. Spot made by blood drop falling vertically 6 feet.

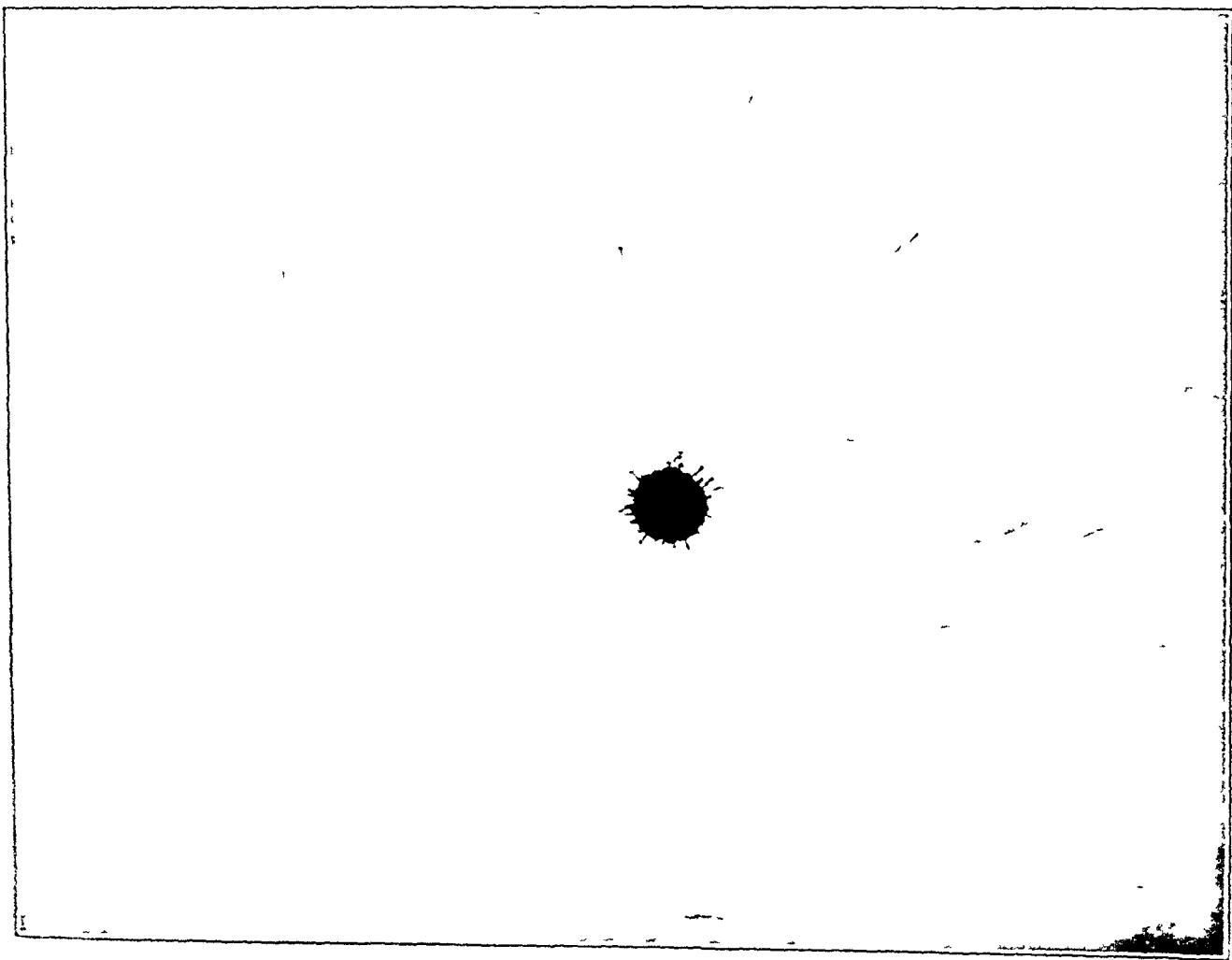


Fig. 11.—White wood planed and sandpapered. Spot made by blood drop falling vertically 1 foot.

might be of some importance, that those from a 6-foot drop would be thrown with so much more force than those from a 3- or 4-foot drop that the former would become more elongated, or that the spatters would be at a greater distance from the drop. But, in fact, it was found that there was no regularity in this respect. As seen in Figures 11 and 12, the few spatters present in the 4-foot drop are rather more elongated than in the 6-foot drop. The 5-foot drop in this series on sandpapered white wood, not shown in the illustration, gave even more spattering and elongation of the spatters than did either the 6-foot or the 4-foot drop on a similar surface. And the 3-foot drop showed as much spattering as either of these two latter did.

We also made a careful study of the spicules in these drops. While in general these become longer the greater the height from which the blood falls, the exceptions to this are numerous. As seen in the illustrations (Figs. 11 and 12), the spicules from the 4-foot drop are fully as long as those from the 6-foot drop in our series on planed and sandpapered white wood. Nor is there any difference in the number or thickness of these by which they are to be differentiated. It appears obvious that neither the degree of spattering nor shape of spatters, nor yet the length or shape of spicules, are of great aid for the purposes for which the tests were made. Within certain limits these depend on the nature of the surface on which they fall, not on the height.

The final test was to find the greatest distance which spatters might fall from the main drop. These distant spatters are so minute that they can only be recognized when falling on some white surface. We used large sheets of white paper, 4 feet, 1½ inches by 6 feet, 3½ inches. The board on which the blood was to fall was placed near the center of a sheet, and a single drop of blood allowed to fall on to it. The spatters on the paper thus not only fell laterally from the drop, but also fell to a slightly lower level, that is about 2 cm. the thickness of the board. Three surfaces were used in this series soft pine, planed, hard pine, planed, wall-paper, pasted onto a smooth board. A drop from four different heights, 3, 4, 5 and 6 feet, was tested on each kind of a surface, and spatters from a single drop obtained on each sheet. The distance of the farthest spatters from the center of the drop was then measured. The results are as follows:

Drop	Soft Pine Most Distant Spatter	Planed Most Distant Spatter	Hard Pine Most Distant Spatter	Planed Most Distant Spatter	Wall Paper Most Distant Spatter
3 foot	37 9		58 8		48 9
4-foot	76 0		51 0		74 8
5 foot	76 1		58 5		73 5
6 foot	63 1		64 0		107 5

Evidently height is of some importance in determining the distance of the spatters, but even here the results are by no means constant, as is seen by comparing the 6-foot drop in the first series with the 4-foot or 5-foot drop, also by comparing the 3-foot drop in the second series with either the 4-foot or the 5-foot drop. Here, again, the nature of the surface, rather than the height, is the main factor in determining the force with which the spatters are thrown.

#### CONCLUSIONS

The conclusions which appear warranted are that a blood-drop falling only a few inches usually makes a round spot with a smooth border, though even here if the surface on which it falls is rough it may have an irregular border with spatters, that when a blood-drop falls vertically whether from a height of only 1 or 2 feet or as much as 6 feet, the height is of only secondary importance in determining the size or shape of the drop or the amount of spattering, that within the limits just mentioned the character of the surface on which the blood-drop falls, particularly as to its roughness or smoothness, is the chief factor in determining the amount of spicule formation and the degree of spattering, that a blood-drop falling vertically 5 or 6 feet on a smooth non-absorbent surface may form almost no spicules or spatters, but that irregularities of the surface may cause marked spicule formation and spattering even when the height has been much less than this, that the size of the main blood-spot made by a drop falling from 3 to 6 feet depends more on the original size of the drop than on the height from which it fell, that the thickness of the layer of blood in dried blood-spots, on surfaces which are non-absorbent or only slightly absorbent is somewhat less the greater the height from which the blood fell, that the height from which blood has fallen cannot be determined by the length of spicules, the elongation of spatters, the distance which spatters have fallen, or by the thickness of the layer of blood, except within wide limits, and that, in general, conclusions as to the height from which blood-drops fell based on any of the appearances of the dried spot, should be made very guardedly.

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# THE EFFECT ON THE KIDNEYS OF TEMPORARY ANEMIA, ALONE AND ACCOMPANIED BY PERfusion

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## INTRODUCTION

As set forth in a previous paper,<sup>1</sup> investigations in this direction were suggested by the character of the results following transplantation of kidneys. To quote "From the results on the kidneys, although my animals lived for several weeks, I came to the conclusion that permanent success was improbable owing to the latter factor" (i.e., injurious effect of the perfusion practiced). The results there reported have since been extended and confirmed, as shown below.<sup>2</sup>

## METHOD

As previously described in the papers cited,<sup>1, 2</sup> the method consists in temporarily shutting off the circulation in a segment of the aorta, including the origin of the renal arteries and then perfusing the kidneys by injecting the solution to be tested into this segment by means of a small trochar (or needle) thrust through the wall of the aorta (Fig. 1), the instrument being connected by means of a rubber tube with a reservoir containing the solution.

On withdrawing the needle the puncture in the wall of the aorta is closed by several simple stitches which penetrate all the coats of the vessel. The clamps (seriesfines) are then removed from the aorta and the abdominal wound closed. The animal is then bandaged and placed in the hospital.

It should be remarked that in addition to the aorta, all arteries other than the renal arising from the segment are clamped, as well as all other vessels that may give a collateral circulation—e.g., the ureters with their surrounding tissues are compressed *en masse* by means of encircling coarse ligatures,<sup>3</sup> which are temporarily fastened by means of ordinary

\* From the Physiological Laboratories of Washington and Pittsburgh Universities.

1 Guthrie, C C Some Physiologic Aspects of Blood vessel Surgery Jour Am Med Assn 1908, li, 1658

2 Guthrie, C C Washington Univ Bull, 1908, viii, 40

3 Narrow strips of cloth are very good for this purpose

hemostatic forceps or sutureines (Fig. 1). Even with such precautions more or less patent arterial connections are maintained as shown by the fact that on withdrawing the perfusion needle, as a rule arterial-hued blood soon begins to escape from the opening.

In some of the experiments the adrenals were shut off by the anterior cerefines and sometimes they were not, so that we have some data on the

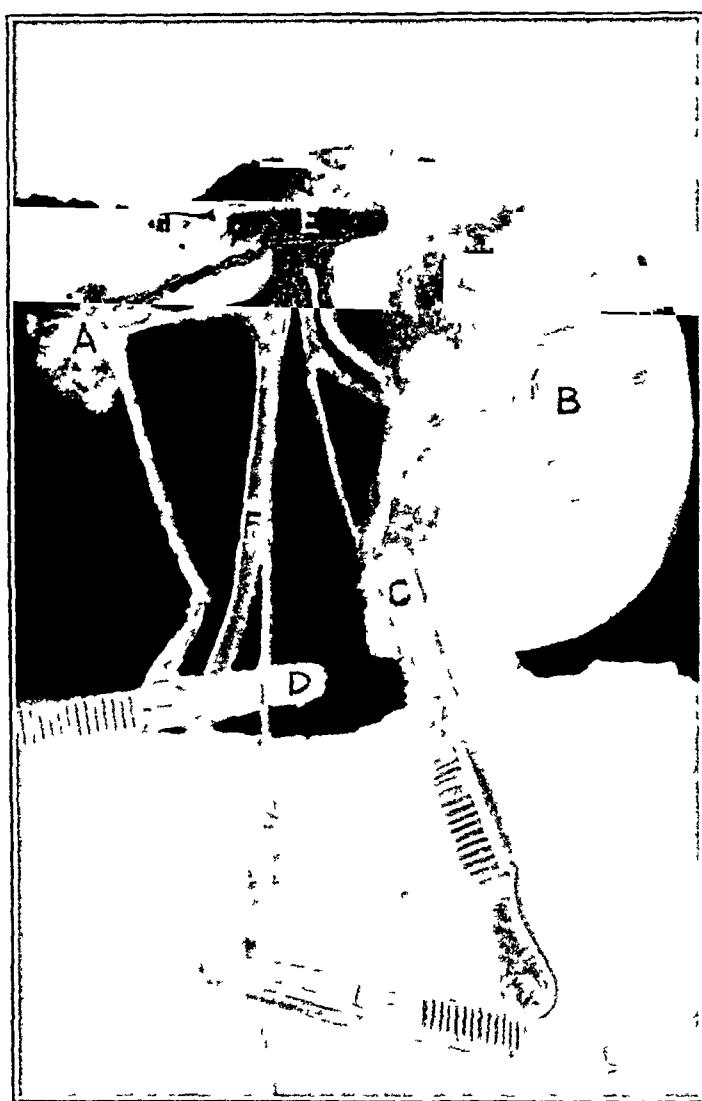


Fig. 1.—Kidneys and aorta of Cat 22, operated on May 23, 1908, photographed May 22, 1909. A right kidney rendered anemic and perfused, B, left kidney anemic only. E and D temporary clamps on aorta. C showing method of clamping ureteral vessels. F perfusion needle, thrust into aorta and connected by tube with reservoir holding solution.

results of perfusing them also. In some cases the renal artery (or arteries) to one kidney was clamped during the perfusion so that it is possible to compare on one animal the result of anemia alone with an-

mia accompanied by perfusion. The temperature of the perfusion liquid varied in different cases, as noted in the table. The pressure employed was, for the most part, practically constant for the non-colloid solutions (plain sodium chloride, Ringer's and Locke's solutions), but with colloid solutions (e.g., starch) more pressure was required to force the liquid

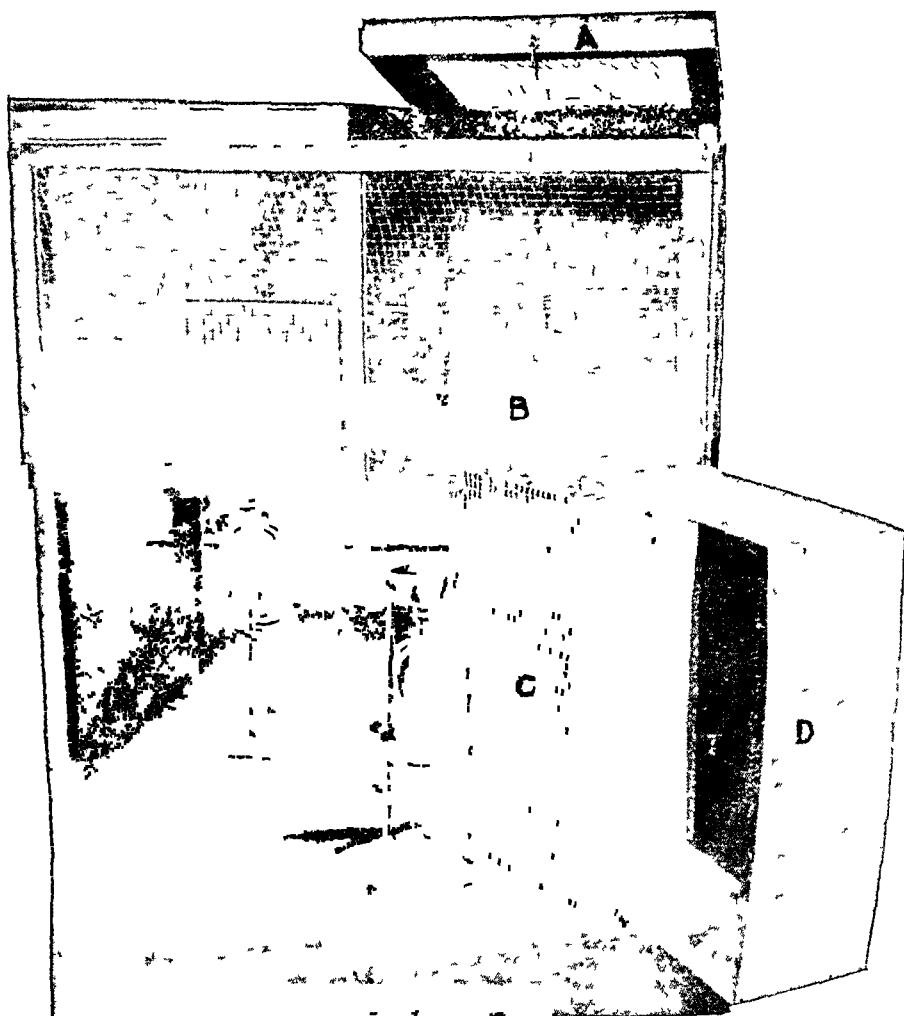


Fig 2.—Practical form of metabolism cage, containing two compartments. Right compartment assembled ready for animal, left dismounted as for cleaning, showing parts, as follows: (A) hinged lid, (B) funnel shaped metal bottom, (C) removable metal screen bottom on which the animal rests, (D) metal guard which fits inside upturned flange on (B), (E) funnel and bottle for receiving urine. Frame finished with waterproof paint. All metal parts galvanized or tinned.

into the capillaries. In those cases in which the urine was collected the animals were kept in metabolism cages along with control cats (Fig 2). The diet, etc. was the same in all cases.

## IMMEDIATE RESULTS

On beginning the perfusion the kidneys could be observed through their capsules to become paler, the degree of paleness being taken as an index of the degree of perfusion. In addition, puncture of the kidneys was made (also through the capsules) with a very fine needle (No. 14

TABLE OF EXPERIMENTS, ANEMIA AND PERFUSION OF KIDNEYS

(Continued from table in Journal of the American Medical Association, 1908, 11, 1658)

No.	Date Operated	Aorta Occluded Min Sec	Period Perfused Min Sec	Solution Perfused With	Death After, Days	Remarks
22	5/23/08	9 45	8 20	Locke's	164*	Anemia of both kidneys Right only perfused
23	5/23/08	12 30	0 0	0	40*	Anemia only of kidney Escaped in July in good condition Showed no symptoms of renal insufficiency
24	11/3/08	22 0	0 0	0	8*	Anemia only of kidney Cat in splendid condition until 8th day when abdominal wound opened owing to absorption of gut suture material, allowing the intestines to escape
25	11/3/08	0 0	0 0	0	25	Ligated renal vessels permanently
26	11/3/08	0 0	0 0	0	6	Excised kidneys
29	12/16/08	20 35	7 0	9 NaCl	84	Partial perfusion only of both kidneys
30	12/16/08	28 0	16 30	Starch	15	Both kidneys perfused
31	12/22/08	16 0	8 0	9 NaCl	131	Left kidney excised See Fig. 7
32	1/26/09	25 0	15 30	9 NaCl	20*	Clot in aorta Some temporary paroxysms Chloroformed after recovery
33	1/26/09	9 0	4 15	9 NaCl	123*	Partial perfusion both kidneys
34	1/26/09	16 30	12 30	9 NaCl	105*	Both kidneys and adrenals
35	1/26/09	11 10	10 0	Locke's	7	Both kidneys and one adrenal perfused
36	1/27/09	10 0	2 15	9 NaCl	122*	Partial perfusion both kidneys Still alive and in fair condition
37	1/27/09	12 30	5 0	9 NaCl	101	Partial perfusion both kidneys and suprarenals
38	1/27/09	10 30	7 0	Locke's	122*	Right kidney removed Still alive in fair condition
39	1/27/09	9 0	5 30	Ringer's	36	Both kidneys perfused
40	1/27/09	11 30	5 30	Ringer's	33	Both kidneys perfused
41	1/27/09	11 15	9 30	Locke's	32	Both kidneys and adrenals perfused
42	2/4/09	18 0	12 0	NaCl	7	Both kidneys and right adrenal perfused
43	2/4/09	19 30	12 0	NaCl	14	Both kidneys perfused Young cat

\* Indicates that the animal escaped was killed or is still alive. This is usually indicated under "Remarks." Nos. 22, 23 and 34 are exceptions. The former is explained in legend under Figure 4, the latter were chloroformed after they became too weak to stand. The amount of liquid perfused varied from about 10 to 100 cc., in general the amount varying with the period of perfusion. In no case, with the possible exception of Cat 30 was the perfusion made with the pressure exceeding an average blood pressure in cats. The solutions were brought to body temperature before beginning the perfusions in most cases but when the room was very cold the temperature of the solution was considerably lowered before it entered the blood vessels. The following temperatures were recorded for No. 30 15° No. 31 37° No. 36 50° No. 38 15° No. 39 20° and No. 41 12° C. These temperatures were taken by allowing the liquid to squirt through the needle on to the bulb of a thermometer.

cannula which was the size usually employed for closing the puncture in the aorta) which permitted a minute quantity of liquid from the blood vessels to escape. By closely observing this liquid as it spread out on the capsule the presence of red blood corpuscles could be observed. It is doubtful whether in any instance was such liquid altogether free of red

corpuscles Our perfusions, therefore, were relatively and not absolutely complete The same was in general true for our anemias, though the amount of arterial blood reaching the kidneys was small—a mere dribble

On releasing the temporarily occluded arteries the kidneys rapidly assume an appearance indicative of a very active circulation The primary recovery of the animal is uneventful One striking feature of the results, though not bearing directly on the major problem may be men-



Fig 3.—Aorta of Cat 32, showing occlusion by thrombus just posterior to renal arteries, kidneys perfused with salt solution, Jan 26, 1909 Cat killed Feb 15, 1909

tioned, viz the result of injury to the aortic intima In two cases only have we observed occluding thrombi in the aorta, and in both these cases the result was due to gross fault in technical procedure connected with the production of temporary hemostasis, by which not only the intima, but the outer walls of the aorta, were crushed and otherwise malfaceted In the first case (Cat 18 reported in a previous paper<sup>1</sup>) the thrombus

extended for some distance both above and below the origin of the renal arteries and the cat died during the first day. The second cat (No. 32) showed partial paralysis of the hind limbs for a few days but this soon entirely disappeared. On the twentieth day the animal was killed with chloroform as its kidneys were desired for examination. Much to my surprise on examining the aorta which is part of the routine of such a post-mortem, the lumen was found to be completely occluded by an old thrombus, beginning 2 to 4 mm posterior to the origin of the renal arteries and extending backward for 11 to 14 mm (Fig. 3). A few days later I received a reprint from Dr. Halsted<sup>1</sup> in which he gives the results of gradual occlusion of the aorta in dogs the occlusion being produced by means of an aluminum band clasped around the vessel by an ingenious

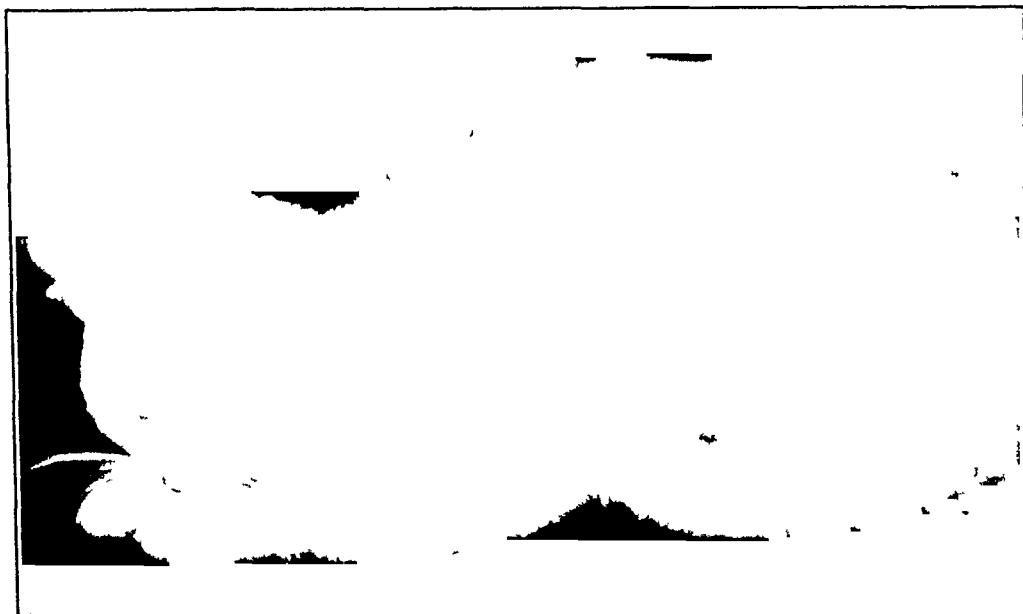


Fig. 1.—Cat 22. May 23, 1908, arterial circulation to both kidneys restrained for 9 minutes 15 seconds. During part of this period the right kidney was perfused with Locke's solution. May 22, 1909, animal photographed and chloroformed (See Fig. 1).

instrument devised by him for the purpose. Essentially the above observations on the cat agree with his observations on dogs. He has observed "in a number of instances about three months after the operation, a deposit of extramural fat about the cord below the site of the aortic band" (p. 377). He promises a full report of the work soon as well as a paper giving the literature and history of the subject.

<sup>1</sup> Halsted W. S. Partial Progressive and Complete Occlusion of the Aorta and Other Large Arteries in the Dog by Means of the Metal Band. *Jour. Exper. Med.* 1909, vii, 373.

## LATER RESULTS ANEMIA ALONE

*Behavior of the Animal*—In the case of anemia alone of the kidneys, or of the kidneys and suprarenals together, no abnormal symptoms were observed and recovery was uneventful. When one kidney was subjected to anemia alone and the other to anemia with perfusion (Cat 22) the result was the same. Anatomically the changes thus far observed have been less marked than when perfusion was practiced.

*Anatomical Changes*—In the case of Cat 22, in which one kidney was rendered anemic, while the other was in addition perfused with Locke's solution, a marked increase in size of the former (compensatory hypertrophy?) with practically complete disappearance of the latter (perfused) kidney was observed 155 days after the operation. Twelve months later the animal was photographed (Fig 4) and then killed with chloroform and the kidneys photographed (Fig 1).

*Histological Changes*—No marked alterations have been observed, but the data on this point are as yet incomplete.

*Chemical Changes*—No studies have been made when anemia alone has been practiced. The metabolism of such animals has suffered no marked alteration, as judged by the condition, behavior, etc. It may be remarked that Cat 22, although having all the appearances of a vigorous male, since the operation seemed to have absolutely no sexual desire, according to the attendant. This seems rather unusual from our experience with cats.

## LATER RESULTS ANEMIA WITH PERFUSION

*Behavior of the Animals*—After anemia with perfusion of the kidneys, cats as a rule show no unusual symptoms for twenty-four hours or more. During this time they appear the same as any cat on which a major surgical operation has been performed. In the acute types of cases the usual symptoms of renal insufficiency rapidly develop, terminating in the death of the animal within a week or ten days, while in the slower types such pronounced symptoms do not appear for weeks or months. In all cases where such symptoms have been pronounced, death has invariably occurred within a few days. As a rule death follows the appearance of such symptoms more quickly in the acute than in the slow types of cases. In the latter especially, the animals usually showed great emaciation before death (Fig 5) or even before the onset of convulsive symptoms. With the onset of convulsions, in all cases death occurred within a few days. Particularly in the acute cases the character and train of symptoms were indistinguishable from the symptoms following

simple ligation of the renal blood-vessels or double nephrectomy. For a day or two preceding death there appeared to be a more or less complete suppression of urine. With the lighter convulsions and during the onset of the stronger ones the pupils usually showed marked constriction but during the height of the stronger convulsions the pupils dilated. It may be remarked that such changes in the pupils are probably due to deficient respiration, it being known that partial asphyxiation produces a constriction (Guthrie and Ryan), followed by a dilatation if the asphyxia be sufficiently complete.<sup>5</sup>

*Anatomical Changes.*—As a rule when examined up to a few weeks after the operation the grosser changes consist in what we have termed a "subnormal resiliency," i.e. the kidneys feel more or less flabby, in appearance they are pale on section the cortex is pale the medulla congested, while in the boundary zone a marked stripe of congestion is seen. The tissue has more or less of the "cooked" appearance that pathologists

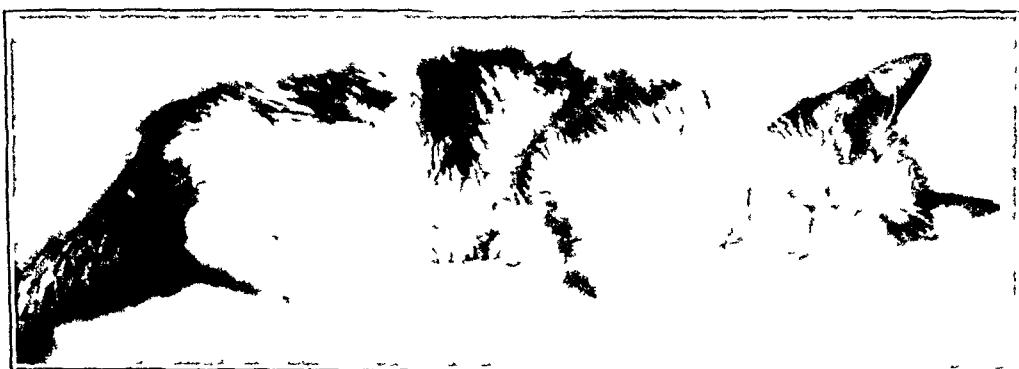


Fig. 5.—Cat 41 photographed shortly before death showing emaciated weak and spasmotic condition. Note the constricted pupils. Jan 27 1909 renal and adrenal arterial circulation restrained for 14 minutes 15 seconds. During part of this period both pairs of glands were perfused with Locke's solution. The animal lived thirty two days.

have associated with parenchymatous degeneration (Fig. 6). Ultimately the kidney becomes harder, and on section less medullary congestion is seen. The cortex is paler than normal.

*Histological Changes.*—The most prominent feature in early examinations is the congestion. This is greatest in the boundary zone and medulla. Later interstitial hemorrhages occur throughout the entire organ. At this stage cloudy swelling of the tubular cells especially is observed. This and the succeeding degeneration is also very marked in the cortex. Cellular infiltration also occurs particularly in the boundary

<sup>5</sup> Stewart Guthrie and Pike. *Jour. Exper. Med.* 1906, viii, 289.

region. The degenerative processes may proceed until cell structure is lost. As a rule, such processes are more marked in certain areas than in others, so that such areas are surrounded by tissue showing more nearly normal structure. Such degeneration may result in the disappearance of Malpighian corpuscles as well as tubules proper.

*Chemical Changes*.—The observations so far have been confined to the urine. At first there seems to be a decrease in the amount of urine. Such urine shows a high specific gravity and a high percentage of normal solids, e. g., urea and chlorides. In the more protracted cases the amount



Fig. 6.—Kidneys of Cat 32, which were perfused with salt solution Jan. 26, 1909. The animal died Feb. 15, 1909, twenty days after perfusion.

and composition may approach the normal for a time, but prior to death another change occurs so that the specific gravity and content of normal solids may sink below the normal.\* Neither albumin nor sugar have been

\* It is interesting to note the composition of normal cat urine. The daily averages for one of our control cats for one week was as follows: Amount 91.4 cc., Sp. G. 1.059, chlorides abundant, urea 17.5 per cent (by the hypobromite method). This figure for urea is unquestionably too high, and I wish to call attention to the fact that the figure given in the table accompanying the paper in the Journal of the American Medical Association (1908, li, 1658) should not be taken as indicating the actual amount of urea present. For some reason as yet unknown to me, the hypobromite method has indicated far too much urea in all cats' urines to which it has been applied. I may say that when time permits, we intend making more thorough analytical studies of the urines, samples of which we have carefully preserved for this purpose.

observed, at least in significant quantities. Since the interpretation of such results is a matter requiring great care owing to the great complexity of factors, e.g., amount and composition of the food eaten, liquids drunk, body weight, physiological state, etc., a more complete discussion is withheld for a later paper. The metabolism appears to suffer great alterations as judged not only by changes in the urine, but by the loss of appetite and of weight and change in general behavior.

#### SUMMARY OF RESULTS

- 1 Anemia alone is apparently much less harmful than when accompanied by perfusion of any of the commoner salt solutions.
- 2 The commoner salt solutions do not seem to differ greatly in toxicity.



Fig. 7.—Cat 31, of which the kidneys were perfused for eight minutes with 0.9 per cent sodium chloride solution, Dec. 22, 1908. Left kidney excised at end of operation. At the time of death, 131 days later, this animal presented a very remarkable thickening of the skin of the head, such as we have never observed before in a cat. There was no indication of it at the time of the operation. We do not necessarily conclude, however, that the condition was due to temporary anemia and perfusion of the kidneys or that the condition itself was solely responsible for the death of the animal.

- 3 Attempts thus far to devise a non-toxic solution for perfusing, e.g., salt-starch solution, have received no encouragement from the results.
- 4 Anemia with perfusion of the kidneys as a rule is followed by death of the animals within a few months—the majority dying in a few weeks.
- 5 The cause of the differences in time of death of the animals are unknown. Individual peculiarities may be (and probably are) an important factor.

6 Metabolic disturbances, seemingly in the direction of increased protein metabolism especially, occur

7 Decrease in urinary secretion preceding death is probably an important factor to consider in interpreting the final symptoms, which are those of uremic poisoning

8 Structural changes of a hemorrhagic and degenerative character occur in the perfused kidneys

#### DISCUSSION

The results show conclusively that renal and adrenal anemia, coupled with perfusion with all the solutions tried, is much more harmful than anemia alone. Anemia alone is certainly not to be looked on as being without effect, but it seems that for cats, under the conditions of these experiments, short periods of occlusion are not incompatible with permanent recovery of the animal. The observations have not yet been carried sufficiently far to enable us to conclude that the life of the animal is not shortened by the anemia. Neither may we conclude that anemia with perfusion as performed invariably shortens the period of life remaining to the animal, for in a few cases, when death did not occur for some months, we cannot be absolutely certain—though the evidence, on the whole, is strongly in this direction—that death was due to the operation. Carrel, in repeating Chirie and Mayer's work<sup>7</sup> on the effect of temporary occlusion of the renal veins on dogs, observed death in one case in a few months after the operation, the period of occlusion being twelve minutes. He attributed death to *ostéo-periostite* of the atlas.<sup>8</sup> But it seems simpler to assume that the operation had a share in the causation of death, since Chirie and Mayer observed epileptiform manifestations and rapid death of dogs in which the renal veins had been occluded for ten minutes. As before indicated, the completeness of the anemia during the period of occlusion is no doubt an important factor, and better control of this may tend to render the results of different investigators more uniform. In addition to this, however, differences in resistance to anemia as well as to anemia with perfusion will probably be demonstrated not only in animals of different species, but in individuals of the same species.

For the present, therefore, it would be unprofitable to discuss the apparent small differences in the toxicity of the solutions used on the cats. Since all solutions seemed to have a toxic action, we may see if a plausible explanation of this action can, with our present knowledge, be

<sup>7</sup> Chirie and Mayer Compt rend hebdomad séances Soc de biol, 1907, LVI, 598

<sup>8</sup> Carrel Comp rend hebdomad Soc de biol, 1909, LVI, 527

given since it is by such theoretical considerations that at least the practical aspects of an experimental investigation are advanced and a conception of the processes at least partially outlined.

Let us consider simple anemia first. In this case not only do the blood-vessels contain a fluid having normal physical properties for the cells of the kidney but it also holds a certain amount of the pabulum for the kidney including oxygen in an available form. Also it is suited to receive a certain amount of the metabolites thrown out by the kidney cells into the blood e.g., carbon dioxide retention of which in the organ is detrimental. Also as before stated absolute hemostasis is difficult to accomplish under the condition of the experiment, so that renal products in the nature of "hormones" may still reach the general circulation, though of course in decreased amounts. However this may be, we must conclude that the factor was in favor both of the simple anemias and of the anemias accompanied by perfusion for it is well known that (1) a tissue receiving a subminimal amount of blood<sup>9</sup> is easier to resuscitate than if the circulation be entirely stopped or if the perfusion be carried out with a blood-free liquid, and (2) that after resuscitation the normality of its subsequent activities will vary directly with the degree and period of anemia.<sup>5</sup>

Indeed it is well known that in simple transplantations of tissues (i.e. without anastomosis of the blood-vessels) results are less perfect when the tissues are treated with salt solution than when subjected to anemia alone (Christiani).

It is interesting at this point to note the work of Polycard<sup>10</sup> who recently has reported in detail the results of an investigation undertaken with the view of determining what structural changes occur outside the body in the epithelial cells of urinary tubules under the influence of sodium chloride solutions of different concentrations. He decapitated white rats quickly removed the kidneys and cut them in very small bits the largest being under 1 mm in thickness. Such fragments were then immersed for fifteen minutes in a salt solution of known strength at a temperature of 15 degrees C. The tissues were then fixed in formaldehyde solution, after which they were prepared for microscopical examination. He concludes that solutions of sodium chloride of all strengths (hypotonic, isotonic and hypertonic) change more or less the cells of the convoluted tubules.

<sup>9</sup> Subminimal being used as indicating in the first instance an amount of blood too small to preserve the ordinary manifestations of activity e.g. in cerebral anemia etc. and in the second instance that the blood is too dilute to preserve such manifestations.

<sup>10</sup> Polycard Jour de physiol et de path gen 1908 x 2

Now, if we examine the salt solutions we find that they all contain one or more of the inorganic salts in approximately the proportion found in the blood. Yet they are all similarly toxic. The same is true of the one containing, in addition to more abundant blood salts (*viz.*, sodium, potassium and calcium), grape-sugar, which is considered another constituent of normal blood. In certain physical characters these solutions differ greatly from blood, or even serum, e.g., they are non-colloidal. Such being the case, we might attribute at least a part of their harmful influence to this factor. To test this point a colloidal solution was prepared by adding boiled starch to a salt solution in such proportion that the freezing point, electrical conductivity and viscosity were nearly identical with normal cat's blood (defibrinated). Yet it was no improvement over the plain salt solution, as judged by the result (Cat 30). But it would be a mistake to draw conclusions from this experiment, as starch is an abnormal colloid for blood. Besides, owing to the cooling of the kidneys during their exposure made for observing the course of the injection (room temperature was 15° C.), it is not improbable that the temperature of the solution was lowered to such an extent that its viscosity was increased. A considerably higher injection pressure was required than for the other solutions, so this, too, must be taken into account. Also, I regret to say, no control experiment was performed to determine the effect of merely introducing it into a cat's circulation. Such experiments are outlined for later performance, as well as the employment of other colloidal solutions, e.g., gum arabic, etc., as well as colloids of animal origin, e.g., serum and milk products. I may add that a salt-starch solution prepared as above, in comparison with plain sodium chloride solution, Ringer's solution and Locke's solution and turtle's blood on strips of turtle's heart, gave results most nearly like the blood itself, *viz.*, on the ventricle it had slight or no stimulating action and the strip retained its irritability well, while on the auricle it sustained the contractions for a longer time than the other salt solutions, and there was also less evidence of stimulation.

A more complete account of the solution will be reserved for future publication, as it is hoped that results with other similar solutions may be obtained and incorporated.

Unlike blood, such solutions lack not only normal physical properties, but they cannot be considered to contain an adequate pabulum—there being no evidence that grape-sugar, which is a constituent of Locke's solution, is adequate in this direction, although it is destroyed by active

tissues<sup>11</sup> Still since the period of anemia is relatively short, and since organs or even cells, like animals, undoubtedly contain a certain amount of material that can take the place of that supplied by the blood for a time, too much stress should not be laid on this point. Even a certain store of oxygen is laid up in the tissues themselves that can be drawn on in such emergency conditions, but there is no evidence that the kidney has a sufficient store to last any great length of time, as is the case in muscle.

Although the solutions employed were well aerated, they contained but a fraction of the amount of oxygen found in arterial blood—indeed, the amount even under pure oxygen is insignificant compared with ordinary venous blood<sup>12</sup>. So we may conclude that the tissues received too little oxygen. Again, the carrying capacity for carbon dioxide of the solutions is far less than that of blood. Also, the total amount of solution injected into kidneys, compared to the amount of blood passing through them normally in the same length of time, is insignificant. We may conclude, therefore, that in anemia with perfusion, as well as in anemia alone, there was a profound decrease in renal respiration, and that this was probably greater in the former than in the latter case. Although some blood probably entered the renal vessels and became mixed with the perfusion solution, the total amount thus entering, considering all other factors as being the same, would be less during perfusion owing to the pressure of the perfusion liquid. Also, such as entered the vessels and became mixed with the solutions probably had a less metabolic value per unit, owing to the dilution<sup>13</sup>. Numerous other possibilities might be brought forward, but what is written above is sufficient to indicate the state and complexity of the problem.

Thirtieth Street and Brierton Avenue

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11 Locke and Rosenheim (*Jour Physiol*, 1907, **xxxvi**, 205), using surviving hearts, observed a more rapid disappearance of dextrose from the perfusion fluid during activity. McGuigan (*Am Jour Physiol*, 1908, **xxi**, 334), working in my laboratory, obtained the same result for skeletal muscle prior to the appearance of Locke and Rosenheim's announcement. So long as the isolated skeletal muscles survive (as indicated by response to electrical stimulation) the sugar disappears. Later, the perfusion fluid filters through the walls of the blood-vessels into the tissues but the sugar contained therein does not appear to be destroyed.

12 Guthrie and Pike *Am Jour Physiol*, 1907, **xviii** 14

13 It is well known from studies on isolated tissues (Cf. Guthrie and Pike *Loc. cit.*) that beyond a certain dilution the addition of blood to an ordinary perfusion liquid is of small value.

# A STUDY OF PNEUMOPERITONEUM

WITH A PLAN FOR ITS DIAGNOSIS

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Pneumoperitoneum cannot be diagnosticated from its physical signs, since any one of these may be present in tympanites. These signs, apparently first recognized by Barth and Roge<sup>r</sup>, are

- 1 A high-pitched, tympanic, often metallic, percussion note, uniform in quality over the entire abdomen
- 2 A diminished or absent area of liver flatness
- 3 A distended, tense abdominal wall
- 4 Embarrassment of the respiratory movements and the heart action

In clinical work the only sign much regarded is the obliteration of liver flatness, and against its reliability there is an increasing array of evidence. Osler<sup>1</sup> has spoken of the probability of its occurrence in tympanites, T. C. Janeway<sup>2</sup> of the proof of this at operation. Spiengel<sup>3</sup> considers it a sign of early spreading peritonitis. McCrae<sup>4</sup> says that if there is any degree of distention no dependence should be placed on it in the diagnosis of perforation of the intestine in typhoid. Cabot<sup>5</sup> believes that distended colon, by rotating the liver upward so that only the thin anterior edge is in contact with the body wall, may obliterate liver dulness. Kircheim,<sup>6</sup> in recent experimental work on cadavers, finds absence of liver dulness both in the relaxed paralytic condition of the diaphragm of the late stages of peritonitis and also in the opposite or spastic condition of the diaphragm, frequent in early spreading peritonitis. In a further report the same writer<sup>7</sup> presents a clinical study of the changes in liver dulness, concluding that this may be obliterated by a combined meteorism and rigidity of the abdominal muscles, and that this condition cannot be differentiated from pneumoperitoneum. Surely here is suspi-

1 Osler Practice of Medicine, Edition 2, p 24

2 Personal communication

3 Spiengel Deutsche Chirurgie, Lieferung 46

4 McCrae Osler's Modern Medicine, 11, 132

5 Cabot Physical Diagnosis, Ed 2, p 133

6 Kircheim Ueber das Verhalten der Leberdimpfung bei abdominalen Erkrankungen, Verhandl d Kong f innere Med., 1909, p 215

7 Kircheim Ueber das Verhalten der Leberdimpfung bei abdominalen Erkrankungen, Deutsch Arch f klin Med., 1909, xcvi, 594

ction enough cast on this sign to make one wary of depending on it when faced by the serious question of intestinal perforation. Nothing new seems to have been added to the facts available in the study of pneumoperitoneum since 1865, when Baith and Roger<sup>8</sup> first described its signs, and 1874, when Guttmann<sup>9</sup> admitted that it could not with certainty be differentiated from tympanites. This, added to the unsatisfactory nature of the methods of diagnosis of typhoid perforation, led to the following study.

By means of a specially devised apparatus, air in measured volume was introduced into the peritoneal cavities of dogs thoroughly anesthetized by morphin and ether, and of cadavers. Ten observations were made on dogs and four on cadavers. Preliminary to each experiment the absence of gas in each peritoneal cavity was demonstrated by the special method to be described later. The first object of study was the establishment of a relative quantitative valuation of the physical signs of pneumoperitoneum. The results of observation on the living animal were so uniform that, for the sake of conciseness, the average figures of the ten experiments are alone given.

The average weight of the dogs was 11 kilos. The first sign of free gas introduced into the peritoneal space was the peculiar, high-pitched, metallic slightly liquid gurgles and bubbling sounds heard with the stethoscope and due to the rapid gravitation of air from among the intestinal coils toward the least dependent parts. When the dog is on its back the air so introduced finds its way very quickly to the epigastrium and beneath the anterior leaves of the diaphragm, between this muscle and the liver. This movement is doubtless hastened by peristalsis and respiration. The second sign to appear was a change in the percussion note. After 50 cc of air had found place in the peritoneal cavity comparison with the previously existing resonance showed a note higher in pitch and of a more tympanitic and very slightly metallic quality. The clinical value of the sign is only relative, and an exact impression of the previously existing resonance would be essential for correct interpretation. One hundred and forty-five cc were enough to obliterate liver flatness. The small amount of free gas necessary to bring out this sign was a source of surprise at first, but is readily understood in the light of Weitz's<sup>10</sup> work on the intra-abdominal pressure. When the animal is in

<sup>8</sup> Baith and Roger. *Traité pratique d'auscultation*, Paris, Ed. 8 1874 (observation made in 1865), p. 688.

<sup>9</sup> Guttmann. *Lehrbuch der klinischen Untersuchungsmethoden*, Berlin, 1874, 355.

<sup>10</sup> Weitz, W. Ueber den intra-abdominalen Druck bei Ascites, *Deutsch Arch f klin Med*, 1909, rev, 257.

the dorsal position, the viscera gravitate toward the posterior wall and give rise to conditions favorable to the production of negative pressure in the least dependent part of the peritoneal cavity—in this instance, the space between the anterior surface of the liver and the anterior body wall—shown in the negative pressure demonstrated in the bladder when the human subject is in the knee-chest position. Obliteration of liver flatness is not sudden, but is marked by certain well-defined stages. During the gradual admission of gas to the peritoneal cavity the percussion note over the liver becomes progressively higher in pitch and more tympanitic in quality, particularly over the thin anterior edge. Soon all dullness disappears over a limited area of the liver lying in the most superior position. This may be but a small area in the epigastrium or about the site of the portal fissure. With continued addition of gas this area encroaches more and more on that of the liver dullness from left to right until the entire liver region becomes tympanitic. The note is now uniform in pitch, quality and intensity throughout the overlying portion of the abdominal wall. This resonance is higher in pitch than that obtained over normal lung, has a slightly metallic quality, and the sensation given the finger is that of a peculiar elasticity.

To alter the contour of the abdomen to an extent appreciable by the eye 205 c.c. of gas were necessary, the appearance of this sign thus following very closely that of obliterated liver dullness. The amount of air causing embarrassment of respiration and heart action was 800 c.c.

Observations on the cadaver were less satisfactory. The size of the individual, the degree of rigor mortis and the occasional presence of gas in the peritoneal cavity as the result of decomposition made accurate data difficult to obtain.

The physical signs caused by the introduction of gas into the peritoneal space appeared in the same order as in the observations on dogs. The amount of gas necessary to obliterate liver dullness varied from 250 c.c. in a small woman, with flaccid abdominal muscles, to 1,000 c.c. in a large man with rigid musculature. Rigor mortis and the absence of peristalsis and respiratory movements probably make these figures higher than would be the case in the living subject.

The absence of liver flatness being for clinical purposes the sole physical evidence of free gas in the peritoneal space, and this being neither delicate nor reliable as a sign, it has seemed desirable that some more delicate test be devised. There is no objection to introducing a trocar into the peritoneal cavity when there is ascites. Carrying this further, there seems no reason why exploratory puncture should not prove the

presence of intraperitoneal gas To have value, such a procedure must be safe, must be readily done, and must give results that are reasonably uniform

The method developed is as follows

The apparatus required consists of a needle of special construction, an ordinary laboratory wash-bottle with perforated stopper and glass tubing arranged in the usual way, half a yard of sound rubber tubing, about 0.25 inch in caliber, a rubber bulb open at either end, and a clip cut-off Given the needle, the whole device may be put together in a moment The ordinary exploring needle is dangerous in the abdomen, the sharp point occasionally, though rarely, tearing the intestine It is also useless in determining the presence of gas, since its lumen is almost always plugged by tissue or exudate when passed through the body wall A needle which is not dangerous to pass into the peritoneal cavity, and one whose lumen remains patent under the conditions of its use, was devised This is a small cannula, the distal end consisting of an obtuse pyramid and having two or more lateral openings placed at unequal dis-

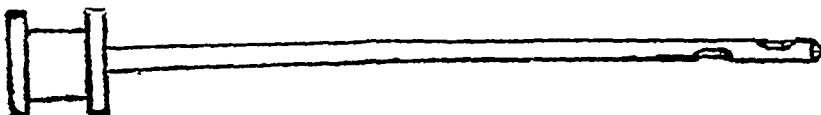


Fig 1.—Exploring needle with two lateral openings

tances from the point (Fig 1) The point is so blunt as to pass through the skin with difficulty and a small incision should be made with a scalpel Once through the skin the other layers of the abdominal wall are easily penetrated and the needle point slipped into the peritoneal space The needle is connected previously with the long tube of the wash-bottle two-thirds full of water, and the air exhausted by suction furnished by the rubber bulb or by the operator's mouth (Fig 2)

If the apparatus before use is proved to be air-tight, the presence of air free in the peritoneal space, even in very small quantity, is shown by the appearance of bubbles from the immersed glass tube A single bubble, or at most two, may be drawn from the apparatus itself, but more than this must have some other source The comparative value of this procedure has seemed the question of highest practical importance The rapid access of gas to the most superior parts of the peritoneal space and its uniform collection immediately beneath the body wall aid in making this direct test of pneumoperitoneum very delicate With the occasional exception of the comparative percussion sign, it is, experimentally, the

most delicate sign of pneumoperitoneum, and was obtained in the average of the observations on dogs after 75 c.c. of air had been forced into the peritoneum, and in every instance considerably before the obliteration of liver flatness.

The safest site for such a puncture is the anterior abdominal wall a little below the level of the umbilicus in the median line or along the external border of the rectus. This is below the great omentum and away from large vessels or solid viscera. It is not necessary for success that the tip of the needle enter a collection of gas. The creation of a partial vacuum in the wash-bottle gives rise to an area of negative pressure about the tip of the needle, toward which point any free gas is immediately drawn. As a refinement of the test a solution of lead acetate may

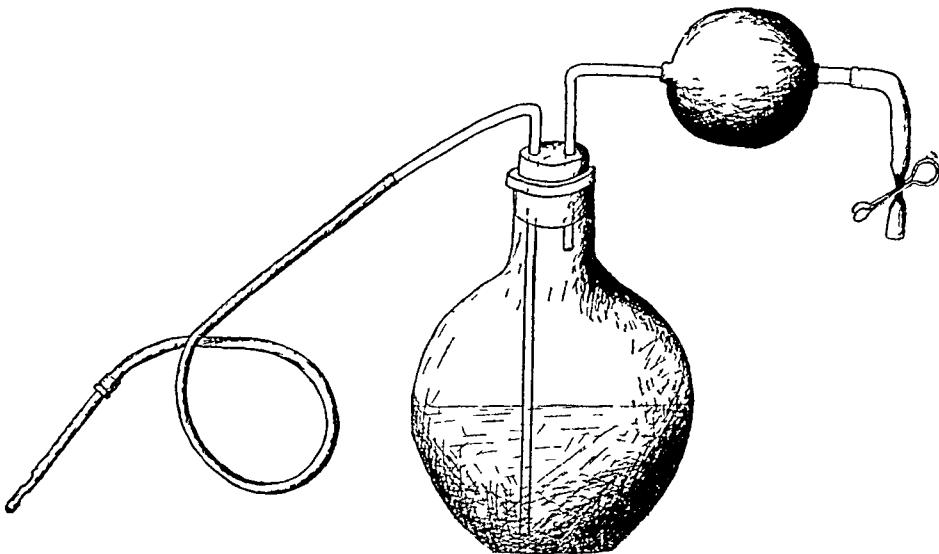


Fig. 2.—Apparatus for exploratory puncture in pneumoperitoneum

be used in the wash-bottle when hydrogen sulphide, if present, would precipitate the black lead sulphide and tend to confirm the intestinal origin of the gas withdrawn.

I have only one clinical report to present, and that negative.

The patient, in the service of Dr T. C. Janeway, at St. Luke's Hospital, New York City, was a man of 20 years, in the third week of typhoid, showing a typical course, until two days before the experiment. At this time there was a sharp abdominal pain and a fall of temperature, a little vomiting, a rise of eighteen beats per minute in the pulse-rate, and an increase in the severity of the general symptoms. The pain ceased, but after two days there was uniform tympany, a little shifting dulness in the flanks and slight tenderness in the iliac fossæ. The liver dulness was not encroached on and the leucocytes were unchanged. Perfora-

tion was suspected and a small exploratory incision under cocaine advised. Exploratory puncture showed no free gas. Incision showed no free gas, or fluid, and no perforation.

The type of case in which an exploratory puncture seems of special value is that showing tympanites preceding symptoms of intestinal perforation.

My thanks are due Prof F C Wood for his courtesy in extending to me the privileges of the laboratory of clinical pathology at the College of Physicians and Surgeons.

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## HEART-BLOCK ASSOCIATED WITH INFECTIOUS DISEASES

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One result of the recent clinical and experimental investigations of circulatory disturbances and of the clearer recognition of the functions of the heart muscle has been an analysis of the various forms of arrhythmia. Diagnosis, prognosis and treatment alike demand that the physician understand, if possible, the pathological physiology of any given instance of cardiac irregularity. A group of cases in which arrhythmia is not infrequent, and in which the determination of the type of arrhythmia is of considerable importance, is that which includes the irregularities of the pulse occurring during and after infectious diseases. While all text-books call attention to the fact that the heart may be irregular in almost any of the infectious diseases, there has been little accurate work, based on cardiographic methods, to show what types of irregularity are most often present. This is doubtless due partly to the fact that, with the exception of arrhythmia dependent on respiration, which may be practically considered as being physiological, irregularities of pulse usually occur when the patient is in too serious a condition to allow the taking of tracings. It is also true, however, that the more grave forms of arrhythmia are not especially common complications of infectious diseases. There is little available evidence on the subject, but in all probability any of the cardiac functions may be affected by the toxins of infectious organisms. One of the most interesting effects, however, is seen in the depression of conductivity—in the production of a partial or complete heart-block.

In a study of the occurrence of disturbances of conductivity depending on infectious diseases, those cases must be omitted in which the length of time between the infection and the production of the cardiac lesion is such that an etiological relationship is improbable, and also those instances in which the type of arrhythmia has not been determined accurately. The literature contains only a comparatively small number of cases of heart-block arising in or following infectious diseases, in which the condition has been proved by graphic records of the venous pulse. Mackenzie<sup>1</sup> reports a case in which he states that the tracings show a

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<sup>1</sup> Mackenzie Brit Med Jour., 1902, n, 1411

complete auriculoventricular dissociation coming on eight weeks after an attack of influenza Joachim<sup>2</sup> reports the case of a man of 24 who developed acute endocarditis and aortic insufficiency after a polyarticular rheumatism, and who showed a partial block for two days A second case was a man of 19 with acute endocarditis and aortic insufficiency in whom the dromotropic disturbance continued for two weeks and was occasionally present afterward A third case of Joachim's<sup>3</sup> was one of acute rheumatism in which a partial block was present for twelve days Jellinek and Cooper<sup>4</sup> reported a case of acute gonorrhreal sepsis in which the pulse became as low as 22, and in which there were intervals of forty seconds without a pulse-beat Autopsy showed an anemic necrosis of the muscular septum in the region of the bundle of His Gerhardt<sup>5</sup> has reported three cases The first was that of a man of 25 years with acute arthritis and fibrinous pericarditis The pulse was intermittent and became as low as 15 per minute At this time the patient had vertigo and loss of consciousness—typical symptoms of Adams-Stokes disease Later the pulse rose to 50-70, and tracings showed a partial heart-block About two months after the onset of the arrhythmia the patient died of typhoid fever, and autopsy showed a cellular infiltration of the bundle of His, with a thickening of the intima of the arteries of the bundle The second case was that of a man of 54, with a well-compensated mitral insufficiency, who had several acute exacerbations of a chronic gonorrhreal arthritis At one time there was evidence of complete dissociation This was followed by partial block and recovery The third case of Gerhardt<sup>6</sup> was that of a girl with acute rheumatism, in whom every third or fourth pulse-beat was dropped out, the irregularity only lasting one day, however James<sup>7</sup> has reported a case of dissociation occurring in a man of 65 during the course of a streptococcus septicemia At autopsy an ulcer was found situated on the interventricular septum, completely destroying the auriculoventricular bundle Bramwell<sup>8</sup> described a man of 29 who developed a complete heart-block during his seventh attack of acute articular rheumatism, which was complicated by disease of the aortic and mitral valves The patient died, and autopsy showed fibrous degeneration of the bundle of His with a calcareous nodule press-

2 Joachim *Deutsch Arch f klin Med*, 1906, lxxxviii, 574

3 Joachim *Ztschr f klin Med*, 1907, lxiv, 95

4 Jellinek and Cooper *Brit Med Jour*, 1908, i, 796

5 Gerhardt *Deutsch Arch f klin Med*, 1908, xciii, 485

6 Gerhardt *Arch f exper Path u Pharmakol*, 1903, li 11

7 James *Am Jour Med Sc*, 1908, cxxxvi, 469

8 Bramwell *Brit Med Jour*, 1909, i, 995

ing on it Rihl<sup>9</sup> reported the case of a man who had had a pulse-rate averaging 30 ever since an attack of acute rheumatism Thirteen years after the attack tracings were taken which showed a complete auriculo-ventricular dissociation There are several instances in which lesions of conductivity have developed late in old rheumatic hearts, but such late manifestations fall outside the present consideration

#### REPORT OF A CASE

The following case was studied in the medical wards of Dr W S Thayer at the Johns Hopkins Hospital

*Patient*—M F (general number, 67,009, medical number, 23,625), a colored boy 16 years old, entered the Johns Hopkins Hospital on Jan 23, 1909, complaining of "general soreness, weakness, and painful joints" The case was diagnosed as acute rheumatic fever and mitral insufficiency Family history was good and patient's past history negative except for pneumonia at 6 years and frequent "sore throat" The patient worked in a "cement gang" on the sewerage system Four days before entrance, on going to bed, he felt a "little sore and achey all over" The next morning his pain was worse It was quite marked in all his joints and in the epigastrium No chills or sweats The pain continued about the same, but had become most severe in the elbows

*Physical Examination*—This shows a well-built, apathetic boy, of good muscular development The anterior pillars of the tonsils are somewhat injected, and the left tonsil is slightly enlarged There is moderate general glandular enlargement The lungs are negative Heart The apex impulse is felt in the fifth interspace 9.5 cm to the left of the mid-sternum The left border of relative cardiac dullness in the fifth space is 11.5 cm from the mid-sternum The right border is just outside the sternal margin On auscultation the heart's action is regular A rather loud, harsh, systolic murmur is heard all over the precordium and transmitted to the axilla The first sound at the apex is rather weak The second sound is louder, and as the patient lies in the left lateral position a third sound is audible following it in early diastole On careful palpation at the apex there seems to be a slight second impulse in diastole, synchronous with the third sound This is more marked during full expiration The second sound in the pulmonic area is accentuated and louder than in the aortic area The abdomen is negative The patient complains of pain on manipulation of the right knee, and, to a less degree, of the left knee The left elbow is painful on motion, and the right elbow slightly so Both hips are painful on motion and tender to pressure There is no swelling or redness of the skin over the joints Palpation over the lumbar vertebrae and muscles is painful Pulse is 92, regular, red cells, 3,936,000, white cells, 16,400, hemoglobin, 75 per cent Temperature on admission is 101, blood-pressure 90 mm Urine examination is negative

*Course of Disease*—On January 26 the pulse rate was 76, and the rhythm was somewhat irregular, the beats coming in groups of four or five For over a week after admission the patient had fever, often reaching as high as 103 The white count remained elevated The pulse ranged from 70 to 90, and later ran from 50 to 60 per minute The type of arrhythmia noted on January 26 only persisted for a few days On February 6, however, after the pulse had been very slow for some time, a second type of irregularity set in This consisted in a more or less

frequently recurring bigeminal rhythm. With the first beat of the pair, a systolic murmur replaced the first sound. This was followed by the normal second sound, but not by a third sound. Instead of the latter, the first sound of the second beat came, and was followed, without any systolic murmur, by a second and a third sound. The patient's general condition improved, his pulse became regular, and he was discharged on February 19.

#### ANALYSIS OF CARDIOGRAPHIC TRACINGS

The tracings taken on January 26 (Figs. 1 and 2) show the heart to be contracting at the rate of 83 per minute. There is a slight irregularity in the length of the brachial pulse-beats and a similar variation in the length of the auricular intervals—from 0.775 to 0.95 seconds. This irregularity undoubtedly falls into the class of "respiratory arrhythmia."



Fig. 1.—Partial heart block. The carotid pulsation participates in the venous tracing. In all figures the upper tracing is the timer, the second is from the jugular vein, the third is the cardiogram, and the lowest is from the brachial artery. The timer marks in tenths of seconds.

Besides this, there are occasional pulse intervals on the brachial tracing which are just about twice as long as the normal interval. These long pauses occur after every four or five beats. Comparison with the apex curve shows that the ventricle did not contract in this interval; it is thus not due to an extrasystole. On some of the apex tracings, however, there is seen, early in the pause, a very slight rise which is found to be almost synchronous with a well-marked wave on the venous curve. This latter is, by the time of its occurrence, undoubtedly a wave of auricular contraction. The long interval between ventricular beats is thus due either to the failure of the stimulus to contract to pass from the auricle to the

ventricle, or to the fact that the excitability of the ventricle was so much lowered that it was unable to respond to the stimulus. Wenckebach<sup>10</sup> has stated that disturbances of excitability are characterized by a normal conduction time. Analysis of the conduction time in this case shows it to

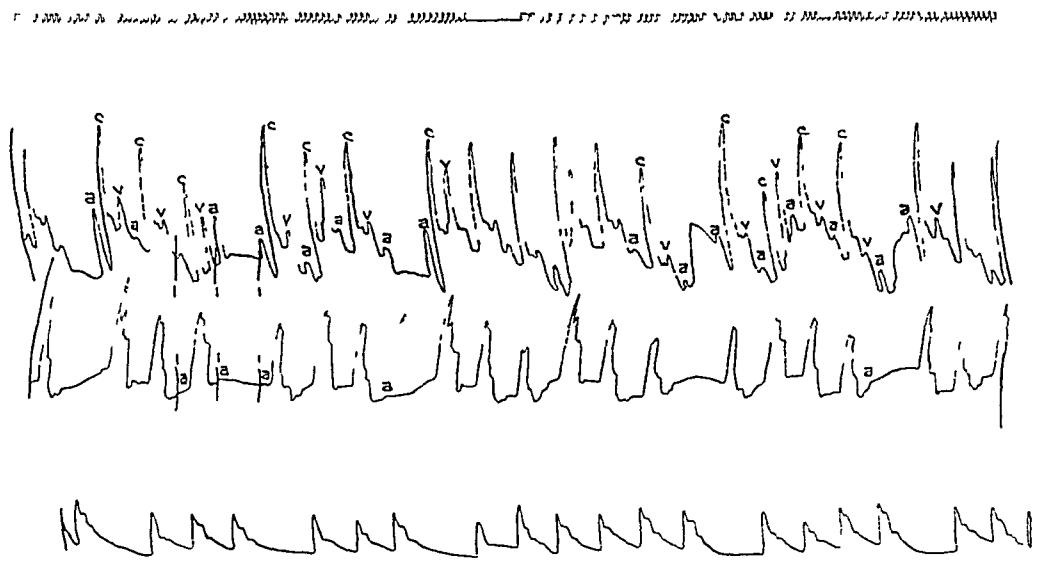


Fig. 2—Partial heart block

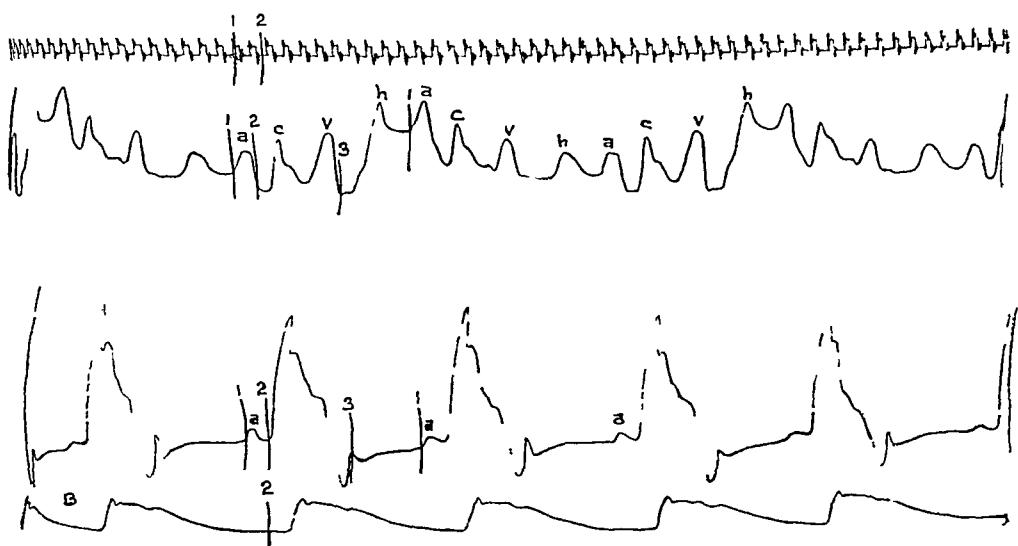


Fig. 3—Regular rhythm with prolonged conduction time. Well marked H wave

be somewhat variable, but in general considerably prolonged. While the normal time between the beginning of the wave of auricular contraction and the beginning of the *c* wave of ventricular systole is usually set at between 0.15 and 0.20 second, the time in this case varies from 0.18 to

10 Wenckebach Arch f Anat u Physiol (Phys abt), 1906 p 297

0.27 second, and is in most instances 0.22 second or more. It is thus evident that the disturbance is one of conductivity, rather than of excitability.

It is frequently characteristic of cases of partial heart-block that the conduction time is shortest after the dropped heart-beat—since the fibers have time to regain their normal power of functioning in the long interval—and that the time increases progressively with each succeeding beat until finally the stimulus fails to reach the ventricle at all, and another beat is dropped out. This sequence of events is not found with absolute regularity in the present instance, but that there is in general an increase in the length of conduction time with successive beats is shown in the following table.

LENGTH OF CONDUCTION TIME OF SUCCESSIVE BEATS IN SECONDS

0.21	0.18	0.26
0.22	0.20	0.26
0.23	0.26	Blocked beat
Blocked beat	0.22	0.20
0.21	Blocked beat	0.24
0.25	0.22	0.27
0.27	0.20	0.22
0.25	0.24	Blocked beat
0.18	0.24	0.20
0.22		

Another point of interest in this tracing, but more clearly shown in those which were obtained later, is the presence of a well-marked early diastolic wave on the cardiogram. This wave, as Thayer<sup>11</sup> has shown, corresponds in time to the occurrence of the third heart sound, is usually found to be well marked in cases in which a third sound is audible, and is probably caused by the early flow of blood from auricle to ventricle.

The condition of partial block was a transient one. On February 2 the heart was regular at a rate of about 50. The conduction time was about 0.25 second. The tracings taken at this slow rate (Fig. 3) show very regularly a well-defined wave about midway between the *v* wave and the following *a* wave in diastole. At times the anacrotic limb of this wave is sharp, but at other times the rise is so gradual that the exact onset is difficult to determine. It falls, however, from 0.28 to 0.44 second before the onset of the *a* wave, and from 0.24 to 0.38 second after the beginning of the *v* wave. While its relations to both *a* and *v* waves are variable, those with the *a* wave appear to be the more constant. The cause of such

<sup>11</sup> Thayer, W. S. Further observations on the Third Heart Sound, THE ARCHIVES INT MED., 1909, iv, 297.

a diastolic wave remains obscure It may perhaps, be considered as what Hirschfelder<sup>12</sup> has described as an *h* wave

On February 3 the pulse was 48 Atropin gr 1/60 was given hypodermically The pulse-rate rose to about 70, but remained regular, showing that even at this more rapid rate the conduction fibers could respond to every impulse The *a-c* time before atropin was given was 0.20 second

On February 6 the pulse was irregular again After deep inspiration, and at times without any cause, there were a series of from two to ten long pulse intervals In some of these a weak beat was palpable at the wrist Auscultation showed, however, that, contrary to the findings previously, the ventricle was contracting in these intervals, but contracting prematurely The arrhythmia at this time was thus obviously extrasystolic The tracings (Fig 4) confirmed this observation On the brachial



Fig 4.—Pulsus bigeminus

curve there is a slight rise during the long interval between the normal beats The apex tracing also shows "pulsus bigeminus" In a tracing where the normal rhythm and the bigeminal rhythm are both present, the longer intervals, in which the extrasystole occurs, are 1.60 seconds long while the intervals between normal beats are 1.2 seconds long The long pauses are thus much less than double the short ones The time from the beginning of an extrasystole to the onset of the next normal pulse wave is 1.05 seconds—just shorter than the normal pulse period These are the relations which are found in extrasystoles of auricular origin The *a-c* time of the first beat of each pair is 0.2 second, or slightly less It is difficult to determine the conduction time of the extrasystole, as the *a*

12 Hirschfelder Bull Johns Hopkins Hosp., Balt., 1907, viii, 265

wave is fused with preceding *v* wave, so that the onset of the *a* wave cannot be accurately made out. There is, however, apparently no shortening of the conduction time at any rate—as there would be if these were auriculoventricular extrasystoles. The venous pulse bears out the conception that the arrhythmia is due to auricular extrasystoles. The same mid-diastolic wave that was present at the slow rate is seen in the longer pauses on this tracing.

The case may be summed up as one of acute articular rheumatism with mitral insufficiency, during the course of which there developed a transient, partial heart-block, and later on an extrasystolic irregularity.

It is interesting to note that of these 12 cases in which there has been proved to be a disturbance in the conduction of the impulse from the auricles to the ventricles, occurring in the course of, or following, an infectious disease, 8 belong to the group of cases which includes acute articular rheumatism and rheumatic endocarditis. From so small a number of cases it is, of course, impossible to draw conclusions as to the comparative frequency of the occurrence of the lesion, but the large percentage tallies well with what one might expect in a disease so commonly associated with cardiac involvement. Mackenzie<sup>13</sup> says "Slight heart-block is of frequent occurrence in cases of mitral disease after rheumatic fever, and even complete heart-block may occur in rheumatic heart affection." There is little absolute evidence as to whether heart-block is met after other infectious diseases, as typhoid and pneumonia. Inasmuch, however, as it has been shown to occur after influenza, there is every reason to suppose that it may occur in them. Butler<sup>14</sup> reports the case of a man whose pulse never had risen above 42 since an attack of typhoid fever twenty years previously. In his final illness the pulse was at times 14, there were pauses between beats up to 20 seconds in length, and he had convulsions. The auricular pulsations were 80 to 130. The case was evidently one of dissociation. At autopsy fatty infiltration and degeneration of the bundle were found. The relation of the dissociation to the typhoid fever is, of course, problematical. Foley<sup>15</sup> has reported a case showing the Adams-Stokes syndrome coming on after an attack of diphtheria, but unfortunately no cardiographic tracings were taken, and there is no note as to venous pulsation, so the evidence that a true heart-block was present is incomplete. In a series of 946 cases of diphtheria, White and Smith<sup>16</sup>

13 Mackenzie Heart, 1909, 1, 23

14 Butler Am Jour Med Sc, 1907, cxxxiii, 715

15 Foley Boston Med and Surg Jour, 1905, clii, 235

16 White and Smith Med Commun Mass Med Soc 1904, viii, 925

found three instances in which the pulse became as slow as 30 to 20, but there is no observation which throws light on the type of bradycardia. The extremely slow rate, however, suggests the ventricular rhythm of a complete block. Mackenzie<sup>17</sup> mentions having seen tracings of mild heart-block obtained from a case of "septic poisoning" and also from a case of puerperal fever. He further states "In acute infections of the heart, writers usually content themselves by mentioning irregularity as one of several symptoms, but the instances cited show that if graphic records were taken, this condition may be found fairly frequent."

An examination into the severity and duration of the symptom in the cases under consideration is of some importance. In the case of gonorrhreal sepsis there was complete dissociation of auricles and ventricles based on an organic lesion, and the patient had frequent convulsions. Death was very probably due to the sepsis, but the cardiac condition must be classed as severe. Gerhardt's case of gonorrhreal rheumatism showed no marked subjective symptoms except for a sudden attack of dyspnea. The cardiac condition, however, was at first one of complete dissociation, and later one of partial block, the whole lasting about a month. Mackenzie's case of influenza showed apparently no special subjective symptoms. The duration of the arrhythmia is not stated. According to Mackenzie, the condition present was one of complete dissociation, but Rihl,<sup>9</sup> in a criticism of the published tracings, does not find enough evidence to assure him that the auricles and ventricles are contracting absolutely independently. James' case, developing on a streptococcus septicemia, was a complete block, and autopsy showed an organic basis.

Turning now to the eight instances of block in association with the "rheumatic series," the striking thing is the mildness of the condition. In five of the cases there were practically no subjective symptoms, and the arrhythmia, which consisted simply in the dropping of occasional beats, lasted only from one day to about two weeks. The other cases of this group are of considerable importance, as they showed much more severe symptoms. While no tracings were taken in Gerhardt's case which demonstrated a complete block, the patient had the typical symptoms of Adams-Stokes disease, and the arrhythmia lasted, with some intermission, for about two months. Death resulted from a hemorrhage in typhoid fever, and an organic lesion involving the system of conduction fibers was found at autopsy. In Bramwell's case tracings showed complete block, and autopsy revealed an anatomical cause for the disturbance. Thus, while in the majority of cases of rheumatic endocarditis in which

17 Mackenzie Diseases of the Heart, London, 1908

a heart-block was found, it was transient and of mild grade, the condition may be severe, and may be dependent on an organic lesion

In considering the direct etiology of disturbances of conduction after infectious diseases, the cases fall into two groups. In four instances, at least, there was an organic basis for the condition. Anemic necrosis, cellular infiltration, ulcer and fibrous degeneration involving the bundle of His were the conditions found. All of these were severe cases. In the milder transient cases, while the condition might depend on a slight inflammatory reaction, it seems improbable that there was any organic lesion at fault. The condition is probably functional, and the obvious explanation of it is that it results from the action of the vagus nerve. It is well recognized that some of the most common postfebrile circulatory manifestations are dependent on vagus hypertonicity. In its more

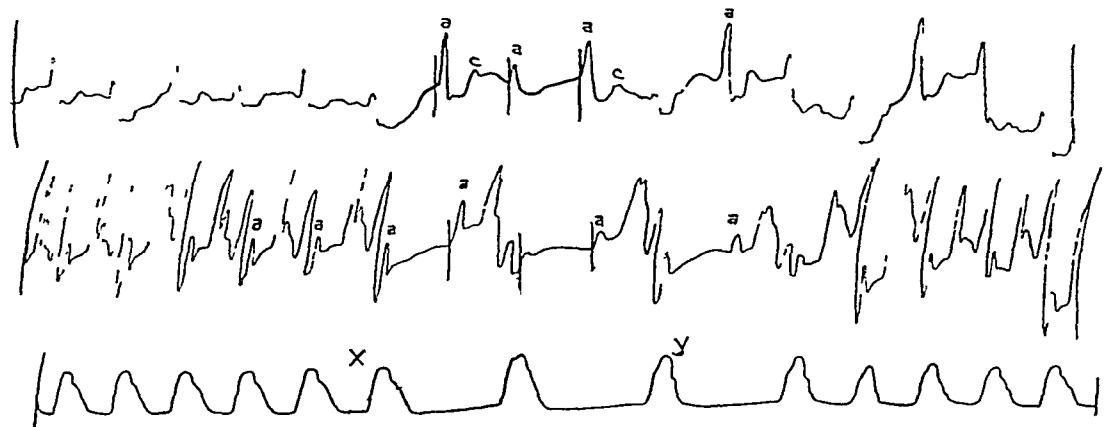


Fig. 5.—Partial heart-block produced by pressure over vagus nerve. Pressure began at X and stopped at Y. (Case to be reported later.)

simple forms vagal activity shows itself in the bradycardia of convalescence, so commonly seen in typhoid fever, and in the so-called "infantile type" of arrhythmia, where the pulse-rate varies with the stage of respiration. In both of these instances it is essentially the chronotropic function of the heart—the rate of stimulus formation—which is affected. It has been shown however, both clinically and experimentally, that stimulation of the vagus nerve may act on the dromotropic function also, and may cause an increase in the time necessary for the stimulus to contraction to pass from auricle to ventricle. If the "conduction time" is sufficiently prolonged the stimulus to contraction may reach the ventricle during a refractory period so that the ventricle cannot respond and one

of the ventricular beats is dropped out. Such a partial block is thus merely the next step to the prolongation of "conduction time." The production of heart-block by stimulation of the vagus is well shown in Figure 5. In this case the rhythm was regular, but the conduction time was considerably increased, presumably on account of some lesion of the conduction fibers, and the slightest pressure over the vagus nerve in the neck was enough to cause the dropping of one or two beats. This extreme activity of the vagus is, of course, not seen in persons with normal heart muscles, but it is fairly comparable to the conditions present in the heart during or after an infectious disease. According to von Tabora,<sup>18</sup> stimulation of the vagus alone will only produce a partial block, but the action of the vagus on a poisoned muscle may result in a complete block. Thus it is easily conceivable that in a heart muscle under the influence of bacterial toxins, vagus stimulation might cause a temporary complete dissociation. This was, perhaps, the condition present in Gerhardt's second case, which resulted in recovery. Analogous instances are the cases of Mackenzie<sup>12</sup> in which artificial stimulation of the vagus by means of digitalis produced a partial block in rheumatic hearts. It is also interesting to note in this connection another quite distinct form of vagus activity to which Belski<sup>19</sup> has called attention as occurring during infectious diseases, and especially in acute articular rheumatism. The condition described by him is a bradycaidia associated with a change in the place of origin of the stimulus to contraction, so that the auricles and ventricles contract absolutely or nearly synchronously. This *atrio-ventriculare Automaticie* he considers to be dependent on the action of the vagus nerve.

In conclusion, one may say that disturbances of the function of conduction in the heart muscle are at least occasionally met with after infectious diseases. They probably occur more often than is generally recognized, and are perhaps most frequently met in cases of the "rheumatic series." The disturbance may be either complete or partial. Complete block is due in most instances to an organic lesion of the conduction fibers, but may, apparently, be due in part to nervous influences. Partial block is usually transient, and is probably due to the action of the vagus nerve on a poisoned myocardium. The prognosis depends chiefly on whether the underlying cause is organic or functional.

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18 Tabora, von Ztschr f exper Path., 1906, III, 499

19 Belski Ztschr f klin Med., 1909, LVIII, 515

## BACTERIOLOGICAL STUDIES ON PARATYPHOID A AND PARATYPHOID B

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### INTRODUCTION

The bacteriological investigations of the last decade have shown that the Eberth-Gaffky bacillus is not the only organism which causes a general infection with fever, roseolar eruption, enlarged spleen, diarrhea, tympanites and abdominal tenderness. Other bacteria, namely, paratyphoid bacilli and general infection with the *Bacillus coli communis*, give rise to clinical manifestations difficult, if not impossible, to differentiate from true typhus abdominalis.

Paratyphoid fever has come to be important, because it has been found to prevail wherever typhoid fever occurs. Epidemics of general infection by the *Bacillus coli communis*<sup>1</sup> are very rare, only one has been recorded. Paratyphoid fever is an acute infectious disease, running a clinical course which resembles typhoid fever in some cases, in others it is chiefly characterized by a diarrhea resembling cholera nostras. The mode of the infection is the same as in typhoid fever, but food infection plays a more important rôle in paratyphoid type B than in typhoid fever.

Bacteriological investigations show paratyphoid bacillus to be distinctly different from the Eberth-Gaffky bacillus. Achard and Bensaude<sup>2</sup> were the first to recognize paratyphoid fever as a different disease from typhoid fever and to discover and describe the organism, naming it paratyphoid bacillus.

They reported two cases. The first was that of a young woman presenting symptoms like those of mild typhoid fever, the temperature was only slightly elevated but lasted forty-six days. During the entire course of the disease there was no leucocytosis, and the Widal test was always negative. From the urine, taken under aseptic precautions a bacillus was isolated which fermented grape-sugar, but did not coagu-

<sup>1</sup> De Haan and De Jonge Laborat. Weldobreden Medeelingen Batavia, 1902

<sup>2</sup> Achard and Bensaude Infections paratyphoidiques Bull et mém Soc méd d Hôp de Paris, 1896, VIII, 820

late milk. Blood-cultures were always negative, the above-mentioned bacteria could not be isolated from the feces. The patient's serum agglutinated only the bacilli which were isolated from her urine. Albuminuria continued long after the pus disappeared from the urine and a diagnosis of pyelonephritis was made.

The second case was that of a seven-year-old child, suffering with bronchitis and a high fever, the bronchitis subsided early in the disease, but the fever continued high until the twentieth day and then fell by lysis.

On the thirteenth day a painful swelling developed over the right sternoclavicular articulation, there was a marked reddening and later fluctuation, the swelling was incised and a small amount of pus which probably came from the joint was evacuated. Cultures from the pus showed micro-organisms identical with those isolated from the first case. Agglutination tests were not made. The micro-organisms isolated from both cases were short bacilli with round ends, ten or twelve flagella, and very actively motile.

The growth on bouillon, gelatine and milk was similar to the Eberth-Gaffky bacillus, the growth on potato resembled *Bacillus coli*, but produced no indol, in glucose-bouillon showed gas-formation, lactose was not fermented.

The serum of immunized animals agglutinated only this organism and had no influence on typhoid bacilli or *Bacillus psittacosis*. The organisms were not so virulent for laboratory animals as the *Bacillus psittacosis*.

Millianne<sup>3</sup> identified both cases as psittacosis infection.

The *Bacillus psittacosis* was isolated in 1892 by Nocard<sup>4</sup> during an epidemic in Paris which resulted from the importation of several thousand parrots from South America suffering with the disease. The clinical picture of "psittacosis" is that of infectious pneumonia. Widal and Nobecourt<sup>5</sup> in 1897 described an organism which they isolated from an abscess in the neighborhood of the thyroid gland, this bacillus was the same as psittacosis except that it was not agglutinated with psittacosis serum. He named this *Bacillus paracoli*, Gilbert<sup>6</sup> suggested that this

3 Millianne Thesis, Paris, 1897

4 Nocard and Leclainche Maladies microbiennes, Paris, 1903

5 Widal and Nobecourt Semaine méd., 1897, pp 285 and 333

6 Gilbert and Fournier Contribution à l'étude de la psittacose Bull de l'Acad de méd., Paris, Oct 20, 1896 Gilbert and Fournier Le Bacille de la psittacose Compt rend Soc de biol., Dec 12, 1896 Gilbert and Fournier Etude sur la psittacose Press Méd., Jan 16, 1897 Gilbert and Leon Contribution à l'étude des bactéries intestinales Compt rend Soc de biol., March 13 1893

bacillus takes a place half-way between the Eberth-Gaffky and the *Bacillus coli communis*. The paracolon bacillus was agglutinated by the patient's serum in the dilution of 1 1,000.

In 1898 Gwyn<sup>7</sup> reported from Osler's clinic a case with all the clinical symptoms of typhoid fever, from which he isolated a bacillus from the blood which was similar to Widal's paracolon bacillus, glucose was fermented by it, but lactose was not, the growth on potato was the same as that of *Bacillus coli*. The patient's serum agglutinated this bacillus in a dilution of 1 200, but did not agglutinate typhoid bacilli in a dilution of 1 5. His diagnosis was paratyphoid fever.

In 1900 Cushing<sup>8</sup> described an organism which he called bacillus O, he isolated it from an abscess that formed at the junction of a rib and costal cartilage. The abscess developed after the patient recovered from an illness that probably was typhoid fever. The patient's serum agglutinated this "bacillus O" in a dilution of 1 800, cultures of it showed very little difference from Gwyn's paracolon bacillus. The serum from Cushing's case did not agglutinate the Gwyn bacillus.

Schottmueller,<sup>9</sup> in 1900, reported a case similar to Gwyn's. In 1901 he reported five more cases, one was a case of para A infection, the others of para B. He called the organism which he isolated paratyphoid bacillus. His work was independent of Achard and Bensaude, of their investigations he had no knowledge at that time. In 69 cases of fever accompanied by abdominal symptoms he found six to be cases of paratyphoid, that is about 4 per cent. All of these paratyphoid cases occurred sporadically and the connection between them could not be found. Schottmueller suspected that the germs were carried by the drinking-water. Clinically it was impossible to differentiate these cases from typhoid fever. According to their action and appearance on different culture media, Schottmueller divides paratyphoid bacilli into two groups. Those in the first group show a continuous acid reaction in litmus milk and produce an invisible growth on potato, the second group at first show

7 Gwyn Infection with a Paracolon Bacillus in a case with All the Clinical Features of Typhoid Fever Bull Johns Hopkins Hosp, 1898, ix, 54

8 Cushing A Comparative Study of Some Members of a Pathogenic Group of Bacilli of the Hog Cholera or *Bacillus enteritidis* (Gartner) Type, Intermediate Between the Typhoid and Colon Groups, With a Report of a Case Resembling Typhoid Fever, in Which There Occurred a Postfebrile Osteomyelitis Due to Such an Intermediate Bacillus Bull Johns Hopkins Hosp, 1900, p 156

9 Schottmueller Ueber eine das Bild des Typhus bietende Erkrankung hervorgerufen durch typhus-ahnliche Bacillen Deutsch med Wehnschr, 1900, p 511 Weitere Mittheilungen über mehrere das Bild des Typhus bietende Krankheitsfälle, hervorgerufen durch typhus-ahnliche Bacillen (Paratyphus) Ztschr f Hvg u Infectionen krankh, 1901, p 368

acid reaction, later alkaline, in litmus milk, the growth on potato is like *Bacillus coli*, forming a grayish-yellow coat

From his clinical experience, Schottmueller concludes that paratyphoid is a milder disease with a more favorable prognosis than typhoid fever. Not one of his patients had a relapse. He states that the blood examination is of great value and that Widal's test and examination of feces are always negative early in the disease.

About the same time, and independent of Schottmueller, Kurth<sup>10</sup> reported five cases of typhoid-like disease, which showed no Widal reaction. In one case he isolated from the feces, in another from the urine, a bacillus which was agglutinated by all the patients' serum. This bacillus fermented grape sugar, produced no indol and did not coagulate milk. Kurth thought that this bacillus was related to the bacillus of Gartner. The majority of reported cases of paratyphoid diseases have been due to infection with the paratyphoid B bacillus, about a thousand of such cases have been observed.

#### REVIEW OF LITERATURE ON PARATYPHOID B

The first epidemic of paratyphoid B fever reported occurred at Saarbrucken, Germany, in 1902, and the cases were systematically investigated by Conrad, von Drigalski and Juergens,<sup>11</sup> Huhnermann,<sup>12</sup> Priefer<sup>13</sup> and Juergens.<sup>14</sup> Thirty-eight cases were observed in the Saarbrucken epidemic, at the same time there were twelve sporadic cases in the surrounding country. The bacillus was present in the feces of eighteen of the epidemic cases and in the feces of all the sporadic cases. All cases reported before the Saarbrucken epidemic occurred sporadically. Sometime later De Feyfer and Kayser<sup>15</sup> reported a small epidemic in Eibergen, Holland, there occurred fourteen cases which ran a clinical course somewhat similar to typhoid fever. The diagnosis was made by agglutination tests only, using the patient's serum and paratyphoid B bacilli. No attempt was made to isolate the organism from the blood.

<sup>10</sup> Kurth Ueber eine Typhus ähnliche, durch einen bisher nicht beschriebenen Bacillus (*Bacillus biemensis febris gastrica*) bedingte Erkrankung Deutsch med Wehnschr, 1901, p 501

<sup>11</sup> Conrad, von Drigalski and Juergens Ueber eine unter dem Bilde des Typhus verlaufende, durch einen besonderen Erreger bedingte Epidemie Ztschr f Hyg u Infectiouskrankh, 1903, p 141

<sup>12</sup> Huhnermann Bacteriologische Befunde bei einer Typhusepidemie Ztschr f Hyg u Infectiouskrankh, 1902, p 522

<sup>13</sup> Priefer Aetiologie, Incubationszeit und klinische Krankheitsscheinungen bei einer Typhusepidemie Ztschr f Hyg u Infectiouskrankh, 1903, p 23

<sup>14</sup> Juergens Zur Aetiologie und Pathogenese des Abdominaltyphus Ztschr f klin Med, Berlin, 1904, Heft 2

<sup>15</sup> De Feyfer und Kayser Munchen med Wehnschr, 1902, Nos 40 and 42

Beljaeff<sup>16</sup> and Zupnik and Posner<sup>17</sup> reported 9 cases, and Lentz<sup>18</sup> 120 cases Vagedes,<sup>19</sup> Friedel,<sup>20</sup> Lembke,<sup>21</sup> B Fischer,<sup>22</sup> Brion and Kayser,<sup>23</sup> Hetsch,<sup>24</sup> Levy and Fornet<sup>25</sup> have reported a great number of cases of paratyphoid B fever, the diagnosis made by agglutination tests and recovering the bacillus from the feces. From a review of all the paratyphoid B cases it appears that paratyphoid B bacilli can be isolated from the stools without any difficulty when Loeffler's malachite-green agar is used, this is in contrast to the difficulty of finding the Eberth-Gaffky bacillus in the stools. The investigations of Conradı, von Drigalski and Juergens during the Saarbrucken epidemic showed that the bacillus may be found in the stools during the first week of the disease, in some cases the bacillus cannot be isolated from the feces, while in other cases it is present for a long time after all symptoms have disappeared. The bacillus was isolated from the stools by Friedel<sup>26</sup> and Lentz<sup>27</sup> two and a half and nine and a half months after all symptoms of the disease had disappeared. Cases in which the paratyphoid B bacillus is present for a long time after the disease, have no other bacteria in the feces, this rule is the same after typhoid fever. The bacillus was present in the urine in only a few cases (Achard and Bensaude,<sup>2</sup> Kuith,<sup>10</sup> Conradı, Drigalski, Juergens,<sup>11</sup> B Fischer<sup>22</sup>)

16 Beljaeff Ueber Paratyphuserkrankungen, Section fur Bacteriologie der kaisserlichen Gesellschaft fur Naturkunde, Ethnologie und Anthropologie in Moskau Sitzung, Nov 2, 1902 Centralbl f Bakteriol, 1903, p 87

17 Zupnik and Posneı, A Typhus und Paratyphus Prag med Wehnschr, 1903, No 18

18 Lentz Ueber chronische Typhusbacillenträger Klin Jahrb, 1905, p 475

19 Vagedes Paratyphusbacillen bei einer Mehlspeisenvergiftung Klin Jahrb, 1905, p 517

20 Friedel Die Typhusuntersuchungen des Laboratoriums der Koenig Regierung in Coblenz Hyg Rundschau, 1906, p 521

21 Lembke Eine Paratyphusepidemie im Kreise Kreuznach Ztschr f Med iesinalbeamte, 1905, p 233-242

22 Fischer, B Untersuchungen über den Unterleibstyphus in Schleswig-Holstein Klin Jahrb, 1906, No 1, p 61

23 Brion A, and Kayser, H Neuere klinisch-bacteriologische Erfahrungen bei Typhus und Paratyphus Deutsch Arch f klin Med, 1906, pp 525-551

24 Hetsch Choleraverdächtige Brechdurchfallerkrankungen und Todesfalle im Spreewalde (Kreis Kottbus) im Jahre, 1905 Klin Jahrb, 1907, p 267

25 Levy, L, and Fornet, W Nahrungsmittelvergiftung und Paratyphus Centralbl f Bakteriol, 1906, pp 161-173

26 Friedel Die Typhusuntersuchungen des Laboratoriums der Koenig Regierung in Coblenz Hyg Rundschau, 1906, p 521

27 Lentz, O Ueber chronische Typhusbacillenträger Klin Jahrb, 1905, p 475

Finding the paratyphoid B bacillus in the blood-stream is conclusive evidence that it is the cause of the disease, recovering it from the feces only is a probable, but not positive indication. Of all the cases observed in Europe, in only a few was the blood examined for the bacillus Jochmann, two cases,<sup>28</sup> Korte,<sup>29</sup> one case, Rolly,<sup>30</sup> two cases, Brion and Kayser<sup>28</sup> and Kayser,<sup>31</sup> three cases, Ruediger,<sup>32</sup> three cases, and Schottmueller,<sup>33</sup> four cases.

The bacillus can be found in the blood during the first days of the disease. Schottmueller found it on the fourth, tenth and fifteenth days of the disease, Korte on the twentieth, Rolly on the seventh and ninth, and Brion and Kayser on the fifth, sixth and seventh days. During the Saarbrücken epidemic the paratyphoid B bacillus was isolated from the rose spots of four patients on the sixth, seventh and eighth days by Comadi, Drigalski and Juergens.

The gall-bladder is the most favorable portion of the body for the growth of this organism, and in it the bacillus is harbored in those cases which show the bacillus present in the feces long after the subsidence of the disease. During life the bacillus has been found in the gall-bladder, in abscesses and in the lochia. Post mortem it has been found in the ventricular and spinal fluids, milk, heart-blood, tonsils, intestine, gall-bladder, spleen, liver and kidneys.

Cases of mixed infection by typhoid and paratyphoid B have been reported by De Feyfer and Kayser, Comadi and Gaethgens,<sup>34</sup> they based their diagnosis on agglutination tests and stool examinations, but neglected to make bacteriological blood examinations and failed to carry the cultivation on various media as far as is necessary to make a differential diagnosis.

28 Jochmann, G. Bacteriologische Blutuntersuchungen, Vortrag in der Sitzung d med Section d schles Gesellsch f vaterlandiche Cult Referat, Centralbl f Bakteriol 1903, p 193

29 Korte, W. Ein Beitrag zur Kenntniss des Paratyphus Ztschr f Hyg u Infectionskrankh, 1903, p 243

30 Rolly Zur Kenntniss der durch das sogenannte Bakterium Paratyphi hervorgerufenen Erkrankungen Deutsch Arch f Klin Med, 1906, p 595

31 Kayser Ueber die einfache Gallenohre als Anreicherungsmittel und die Bacteriologie des Blutes bei Typhus sowie Paratyphus Munchen med Wchnschr, 1906, No 17

32 Ruediger Bacteriologic Study of the Blood in Thirty Cases of Clinical Typhoid Fever Tr Chicago Path Soc, Jan 12, 1903

33 Schottmueller Ueber eine das Bild des Typhus bietende Erkrankung hervorgerufen durch typhus ahnliche Bacillen Deutsch med Wchnschr, 1900, p 511 Weitere Mittheilungen über mehrere das Bild des Typhus bietende Krankheitsfälle, hervorgerufen durch typhus ahnliche Bacillen (Paratyphus) Ztschr f Hyg u Infectionskrankh, 1901, p 368

34 Gaethgens, W. Ueber einen Fall von Mischinfection von Typhus und Paratyphus Centralbl f Bakteriol, 1906, No 5

## CLINICAL COURSE OF PARATYPHOID B

One-half the cases run a clinical course which resembles that of mild typhoid fever, the other half clinically resemble Asiatic cholera. Of the typhoid-like cases, 50 per cent start with headache, anorexia, malaise and fatigue, which gradually grow more severe, so that the patient is compelled to take to bed from fourteen to twenty-one days after noticing the first symptom, the same as in typhoid fever. The others have a sudden onset, if the patients are adults they are seized with a chill, which is followed by a sudden rise of temperature to 40 or 42 C., and sometimes vomiting, in children the chill does not occur, but the onset is marked by convulsions. Herpes of the nose and lips may appear in the first hour of the disease. Diarrhea is present throughout the illness in 70 per cent of the cases. The stools are dark brown, pulaceous, and have a peculiar odor. Feces never have the appearance of pea-soup. A roseolai rash appears the same as in typhoid, when abundant it is punctate, when scanty it is more macular.

In some cases, those of sudden onset, the highest temperature is registered on the first day. When the onset is gradual the temperature-curve is similar to that of typhoid fever during the first three or four days of the disease. The duration of fever after the fourth day is variable, anywhere from three days to three weeks, during which time the temperature-curve shows daily oscillations of two or three degrees C. From the sixth to the twenty-fourth day of the disease, the temperature begins to recede by lysis, and about seven days later is normal. Some observers have pointed out, as an aid to differential diagnosis, that in typhoid fever the enlarged spleen is usually palpable and soft, while in paratyphoid fever B the spleen is palpable in only 20 per cent of the cases and is hard. The mortality of paratyphoid B fever cases which run a course resembling typhoid fever, is less than that of paratyphoid B fever cases which resemble Asiatic cholera and meat-poisonings, it is also less than the mortality of typhoid fever, but more than the mortality of paratyphoid A fever. During the Saarbrucken epidemic, 30 cases, there were no deaths. Lentz reported 120 cases, with a mortality of 33 per cent, the mortality of paratyphoid B, choleraiform type, at the same time, was 9 per cent. The cases of paratyphoid B fever caused by meat poisoning and some cases infected in other ways, are of this type, which composes about one-half of all the cases of paratyphoid B fever. Clinically, this type of paratyphoid, cholera nostras and Asiatic cholera, are identical, when the latter is prevalent cases of paratyphoid may be confounded with it. The correct diagnosis can be made only by bacteriologic examination. Schottmueller reported 5 cases, which he at

first thought were Asiatic cholera from the clinical picture, but he found the paratyphoid B bacillus and not the comma bacillus in the stools.

A large epidemic of similar cases was observed by Hetsch in Kottbus and vicinity during the autumn of 1905. The course was pernicious and the clinical picture exactly like that of Asiatic cholera. The rice-water stools were fetid and contained mucus and paratyphoid B bacilli. Many similar cases have been observed and reported by Muehlens, and Kutschner,<sup>35</sup> Vagedes, Friedel, Lentz and Rolly.

The mortality of choleric form type of paratyphoid B fever is higher than in any of the other forms of paratyphoid.

TABLE 1—POST-MORTEM FINDINGS IN CASES OF PARATYPHOID B

Reported by	Day of Disease	Spleen	Intestine	Stomach	Mesenteric Glands
Longcope	3	Enlarged	Slightly elevated follicles in the colon	No change from normal	No change from normal
Luksch	12	Slight enlargement	Mucous membrane distended and pale	Mucous membrane showed a few hemorrhages	Enlarged and reddish
Jochmann	18	Swollen	No change from normal	No change from normal Blood contained paratyphoid bacilli	Swollen Blood contained paratyphoid bacilli
Vagedes	2	Normal	Marked swelling of Peyer's patches they contained many paratyphoid bacilli	All organs and feces contained paratyphoid bacilli	All organs and feces contained paratyphoid bacilli
Brion and Kayser	18	Slightly enlarged	Ulcers on Peyer's patches Many ulcers, some as deep as the muscularis, in the ileum, cecum, ascending, and sigmoid flexures		Slightly enlarged and reddish
Rolly	7	Slight enlargement	Injected and edematous superficial ulcer above ileo cecal valve	Mucous membrane red and swollen	No change from normal
Hetsch	Several cases all the same	Slight enlargement	Acute inflammation of small intestine	No change from normal	No change from normal

#### PATHOLOGIC ANATOMY OF PARATYPHOID B

Unquestionable cases of paratyphoid have been examined post-mortem by Longcope,<sup>36</sup> Luksch,<sup>37</sup> Jochmann,<sup>28</sup> Vagedes,<sup>27</sup> Brion and Kayser,<sup>23</sup>

35 Kutschner Abdominal Typhus In von Kolle and Wassermann's Handbuch der pathogenen Microorganismen, Jena, 1906, p 188

36 Longcope, W T Paracolon Infection, together with the Report of a Fatal Case, with Autopsy Am Jour Med Sc, 1902, p 209

37 Luksch, F Ein Beitrag zur pathologischen Anatomie des Paratyphus Centralbl f Bakteriol, 1903, No 34

Rolly,<sup>30</sup> Trautmann,<sup>38</sup> Drigalski,<sup>39</sup> Hetsch<sup>24</sup> and Kutscher, the findings in the cases of Longcope, Luksch, Jochmann, Vagedes, Brion and Kayser, Rolly and Hetsch, are given in Table 1. The number of post-mortems have been too few to draw conclusions from. It is probable, however, that in this disease, as in typhoid fever, there is a characteristic pathological change in some of the organs.

In addition to the changes found in the spleen, intestines and lymphatic glands in paratyphoid fever, there are parenchymatous and fatty changes in the liver, heart and kidneys, the same as in all other infectious diseases (Trautmann, Drigalski and Kutscher).

A summary of the post-mortem findings in Table 1 shows a more or less marked gastro-enteritis in all cases, in contrast to typhoid fever, changes in the lymphatic apparatus are only occasionally observed, and the Peyer's patches are ulcerated in very few cases. In some cases the pathological findings are similar to those of dysentery.

Infection with paratyphoid bacilli is through the gastrointestinal tract.

#### PARATYPHOID B BACILLUS AND THE ETIOLOGY OF FOOD-POISONING

Research has established close relationship between paratyphoid B bacillus and the other bacilli<sup>40</sup> which cause disease after the ingestion of infected food-stuffs. Meat-poisoning usually occurs after partaking of raw or slightly cooked meat, pudding or sausage.

Large and small epidemics have been observed which showed different clinical courses. In most cases the onset is sudden, vomiting and diarrhea occurring immediately after eating the infected meat, other symptoms appearing six or twelve hours later. Occasionally symptoms do not develop until two or three days after ingestion. Sometimes the disease starts like cholera nostras and develops the clinical picture of that disease, about 30 per cent of such cases show great weakness and ataxia. A few cases run a course similar to typhoid fever, the epidemic of Kloten belonged to this group. In others the disease is milder, the symptoms suggesting a simple gastroenteritis.

38 Trautmann Der Bacillus der Dusseldorf Fleischvergiftung und die verwandten Bakterien der Paratyphusgruppe Ztschr f Hyg u Infectionskrankh, 1903, p 139

39 von Drigalski Ueber eine durch Genuss von Pferdefleisch veranlaste Massenvergiftung, Beitrag zur Aetiology der Fleischvergiftung Festschr zu R Koch's 60th Geburtstag, 1903, p 409

40 Nearly all diseases resulting from eating infected food are caused by either paratyphoid B bacillus or the *Bacillus enteritidis* of Gartner, a small proportion are due to an anaerobic organism, very different from the Para B bacillus and *Bacillus enteritidis*, the *Bacillus botulinus* (von Eimengen)

There are two etiologic factors in the acute gastric forms. In addition to the bacteria, there are the toxins formed by them before and after entering the stomach. Those belonging to this group are primarily cases of intoxication, and the sudden onset of choleraiform symptoms are due to the toxins.

The symptoms usually observed are diarrhea, fetid, yellow ejections, toxic albuminuria, herpes, roseola, urticaria and multiple hemorrhages in the skin. Relapse seldom occurs, convalescence is slow, the mortality is between 2 and 5 per cent.

Meats which carry this disease are obtained from animals that were diseased at the time they were slaughtered, and these meats were not cooked sufficiently to kill the bacteria and destroy the toxins. The causes of many epidemics have been traced to the products of cows, calves, pigs and horses affected with septic inflammatory processes, mastitis polyarthritis, phlebitis of the umbilical vein, puerperal and pneumonic processes and unclassified gastrointestinal diseases.

Most of the choleraiform cases occur in the summer after eating raw scraped meat, smoked meat, salt meat or sausage. Often the curing, salting or boiling have not been sufficient to destroy the bacteria. Sausages are especially dangerous, because they are made of the inferior grades of meat, intestine, liver, kidney and lung, and the intestines, livers, kidneys and lungs of diseased animals contain enormous numbers of pathogenic bacteria. The structure of sausage is peculiarly favorable to the development of bacteria and the retention of their toxins, the long time which intervenes between the manufacture and consumption of sausage increases the danger.

Gartner<sup>41</sup> was the first to establish the etiology of this disease. During an epidemic of meat-poisoning he discovered that the patients had all eaten meat obtained from one animal, and he found that the animal had been suffering with gastrointestinal catarrh when it was slaughtered. He isolated from some of the fresh meat and the spleen of the cow a pathogenic organism which he named *Bacillus enteritidis*.

From the spleen of a man who had eaten some of the meat, developed the disease and died, he recovered the same bacillus.

After an exhaustive investigation, Noble<sup>42</sup> divided all the cases of meat-poisoning into two groups, according to their etiology. In the first group are all the cases due to infection by the *Bacillus enteritidis* (Gartner), and the second group contains all the cases that were caused

41 Gartner, Breslauer Aerztl Ztg., 1888

42 De Noble Van Ermengem Fleschvergiftungen in von Kolle and Wassermann's Handbuch der pathogenen Microorganismen, Jena, 1903, II, 657

by the paratyphoid B bacillus Noble's investigations have been confirmed by B Fischer,<sup>43</sup> Trautmann,<sup>48</sup> Boehme,<sup>44</sup> Uhlenhuth,<sup>45</sup> Vagedes,<sup>19</sup> Kutscher and Meinike<sup>46</sup>

TABLE 2—CASES OF MEAT-POISONING, DIVIDED INTO GROUPS ACCORDING TO ETIOLOGY

Group 1		Group 2	
Caused by <i>Bacillus Enteritidis</i> (Gartner)	Epidemic	Caused by <i>Paratyphoid B</i> Bacillus	Epidemic
Observer		Observer	
Frankenhausen	Gartner	Gaustad	Holst
Moorseele	Van Ermengem	Berslan	Fluegge & Kaensche
Gent	Van Ermengem	Posen	Guenther
Bruegge	De Noble	Hatton	Duiham
Brussel	De Noble	Chaddeiton	Durham
Willbroek	De Noble	Sirault	Heiman Van Ermengem
Rumfleth	Fischer	Aertyk	De Noble
Haustedt	Fischer	Meirelbeck	De Noble

The organism which caused all the cases in the second group, named by different observers mouse-typhus bacillus (Loeffler), hog-cholera bacillus and *Bacillus psittacosis* (Nocard), has been proved by cultural and immunisatoric tests to be the paratyphoid B bacillus

At the present time the consensus of opinion of the previously mentioned observers is that the majority of all cases of food-poisoning are caused by the paratyphoid B bacillus

The reported epidemics since 1900 have all been caused by the paratyphoid B bacillus, they are given in Table 3

TABLE 3—EPIDEMICS SINCE 1900

Epidemic	Reported By
Dusseldorf	Trautmann
Kiel	B Fischer
Berlin	Kutscher
Frankfurt a M Hospital	Bingel
Virchow Hospital (Berlin)	
German inf't regt 160th	Maix
Neunkirchen	Drigalski
Greifswald	Uhlenhuth
Halle	Liefmann
German Man of War (Blitz)	Rugge & Rogge

Meat was the principal but not the only foodstuff which carried the disease in those epidemics

The serum from all the cases agglutinated not only the bacillus isolated from the patients, but also all other cultures of the paratyphoid B bacillus, in high and low dilutions

The last six cases in Table 3 occurred during the year 1908

<sup>43</sup> Fischer, B Zur Aetiology der Fleischvergiftungen Ztschr f Hyg u Infectionskrankh, 1902, p 447

<sup>44</sup> Boehme, A Weiterer Beitrag zur Characterisirung der Hog Cholera (Paratyphus) Gruppe Ztschr f Hyg u Infectionskrankh, 1905

<sup>45</sup> Uhlenhuth Zur Kenntniss der gastrointestinalen Fleischvergiftungen und der biologischen Eigenschaften ihrer Erreger von Leuthold Gedenkschr, 1906 p 71

<sup>46</sup> Kutscher and Meinike Vergleichende Untersuchungen über Paratyphus, Enteritis und Mausetyphusbakterien und ihre immunizatorischen Beziehungen Ztschr f Hyg u Infectionskrankh, 1906, p 301

## REVIEW OF LITERATURE ON PARATYPHOID A

It is the prevailing opinion that paratyphoid A is an uncommon disease and of minor importance, because so few cases of the disease have been recognized Chiefly through the efforts of Koch, during the last few years a great many systematic studies of typhoid and typhoid-like cases have been carried out in Germany The majority of those interested in that work believe that paratyphoid B occurs frequently, but that typhoid cases are more numerous They think that the number of cases of paratyphoid A are few and of little importance Kayser believes that paratyphoid A fever is an important disease, worthy of more attention than has been given it in the past

If typhoid and typhoid-like cases were studied in America as they are in Germany, we believe that paratyphoid A fever would be found to occur much more frequently than paratyphoid B, and the number of cases would be found greater than is imagined at present A review of the American literature on paratyphoid fever shows that nearly all the reported cases belong to Group A Cases of unquestionable paratyphoid A fever have been reported in the United States by the following Gwyn<sup>7</sup> (1898, 1 case), Cushing<sup>8</sup> (1901, 1 case), Coleman and Buxton<sup>47</sup> (1902, 1 case), Johnston<sup>48</sup> (1903, 2 cases), Hewlett<sup>49</sup> (1903, 2 cases), and Allen<sup>49</sup> (1903 2 cases) It is remarkable that in 1908-09 we found in the Allegheny General Hospital over 50 cases of paratyphoid A fever,<sup>50</sup> about 200 cases of typhoid fever, but not one case of paratyphoid B

In Germany the following have reported cases Schottmueller<sup>9</sup> (in 1900, 1 case A, in 1901 one case A, and 5 cases of B), in 1901, Brion and Kayser<sup>51</sup> (1 case paratyphoid A), Kayser<sup>52</sup> (2 cases A), and Rolly<sup>30</sup>

47 Coleman, W., and Buxton, B H Paratyphoid Infections with Report of a Case Clinically Identical with Typhoid Fever in Whose Blood Paratyphoid Bacillus Was Found Am Jour Med Sc, 1902, p 976

48 Johnston, W B Paratyphoid Fever, Report of Four Cases, Analysis of All Reported Cases Am Jour Med Sc, 1902, p 187

49 Hewlett, A W Report of a Case of Paratyphoid Fever Am Jour Med Sc, 1902 Allen, H W Paracolon Infections, with Report of Three Cases Am Jour Med Sc, 1903, p 96

50 Proescher, F., and Roddy, J A A Report of Forty-eight New Cases of Paratyphoid Fever, Type A, Jour Am Med Assn, 1909, lxi, 470

51 Brion, A., and Kayser, H Ueber eine Erkrankung mit dem Befund eines typhusahnlichen Bakteriums im Blute (Paratyphus) Munchen med Wehnschr, 1902, No 15

52 Kayser, H Bakteriologischer Befund bei einem weiteren Fall von Paratyphus des Brion-Kayser schen Typhus A Centralbl f Bakteriol, 1905 1906, p 285

1 case of paratyphoid A fever in 1906 Netter<sup>53</sup> reported 17 cases in France, but he did not examine the blood and it is doubtful whether the bacilli were A or B

Strong<sup>54</sup> and Hume<sup>55</sup> reported cases in 1902 as paratyphoid A, but the bacilli produced indol and were not agglutinated by para A serum

R Kasuya is said to have reported a case of paratyphoid in Japan in 1908, but we have been unable to obtain his report or cultures

Cultures from eleven cases, isolated by other investigators, whose names follow, were obtained from Kial of Prag, and have been studied by us Gwyn, Cushing, Coleman and Buxton, Hewlett, Johnstone (patients, Milefsky and Badach), Allen (patients, Samuels and Euster), Schottmueller (patients, Barg and Mueller), Bion and Kayser. A summary of the clinical course, bacteriological findings and agglutination results of these 11 cases is here given

The prodromal period lasted from three to twenty-four days, average 13 days. The onset was abrupt in 3 cases, in others it was gradual, but not so long as for typhoid fever. Ten patients were males, two females, one was a negro and one a negress, all the others were Caucasians. The patients' ages ranged from 16 to 46 years, two were under 20 years, two were in the fourth and one in the fifth decade, the rest were in the third decade of life. The duration of fever was from ten to twenty-eight days, average duration eighteen days. Two patients had relapses which set in after the temperature had been normal for one week, the relapse lasted for ten days in one and fourteen days in the other case. One patient had three fever periods of ten, fifteen and sixteen days' duration, between which were two periods of seven days each when the temperature was normal and symptoms absent. None of the patients had ever had typhoid or paratyphoid before.

*Initial Symptoms*—Headache and general malaise were the first symptoms in all but one case, soon afterward, anorexia developed, half of them had vomiting, 3 developed coryza, 4 were conscious of fever, 2 complained of alternating chilly and feverish sensations, one had cough and white mucous expectoration, one acid eructations and vaginal discharge. One case with abrupt onset started with pronounced chill, fever and sweat. Five patients were constipated, five had mild diarrhea, and in two the bowels were normal.

53 Netter, M M A Quatrième série d'infections paratyphoidiques (23 cases nouveaux) Compt rend Soc de biol, 1905, p 501

54 Strong Paracolon Bacillus Bull Johns Hopkins Hosp, 1905, p 501

55 Hume A New Pathogenic Bacillus Isolated from a Case Diagnosed as Typhoid Fever The Thompson-Yates Laboratories Rep, 1902, iv, 2

*Clinical Course*—All the patients were constipated except one, who had from three to five greenish, watery evacuations daily for twenty days. In the majority the tongue was coated uniformly with a thick grayish-white fur and was moist. Two had typical typhoid tongues, one had a dry, reddish-brown, glazed and fissured tongue. One patient had pharyngitis and one had bronchitis. Dicrotic pulse was noted in only two cases.

Of these 11 patients, 6 had slight abdominal tenderness, one had tympany and distention. The spleen was large and palpable in 10 out of 11 cases. The liver was slightly enlarged in 4. Half of the patients showed slight albumin in the urine. A roseolar rash appeared on 10 out of 11 patients, the individual rose spots were similar, but not as many as in cases of typhoid fever.

The Widal tests were always negative, the diazo reaction was positive in three cases. The average temperature during the height of the disease was between 101 and 102 F., pulse 80 to 90. The highest temperature recorded in most cases was 103, one patient when admitted had a temperature of 105, which fell several degrees in a few hours. All cases ended by lysis, which was preceded in two cases by a pseudocrisis.

Complications developed in 4 cases. 2 patients had delirium for several days, one had cholecystitis and lobai pneumonia, and two patients had intestinal hemorrhages. Convalescence was rapid and recovery complete in all cases.

Cushing's case differs from the rest in being purely surgical and treated as such. Culture taken from the wound showed only one kind of organism, it fermented glucose and did not coagulate milk.

#### OCCURRENCE OF PARATYPHOID A BACILLI

Paladino-Blandini<sup>56</sup> isolated a bacillus which he believed was the paratyphoid A bacillus, from spring-water, used for drinking purposes in an Italian village where typhoid-like cases of fever occurred.

During the three months when the greatest number of cases of paratyphoid fever occurred in Pittsburg, water was taken from the Allegheny and Monongahela rivers at different points in the city and suburbs daily, in all that time neither typhoid nor paratyphoid bacilli were found in it.

Morgan<sup>57</sup> states that he found paratyphoid A bacilli in the feces and scappings from the mucous membranes of the small intestines of healthy guinea-pigs, rabbits, pigs, sheep and horses. The organisms isolated and

56 Paladino Blandini Contributo alle conoscenze sui paratifi Ann d'ig sper 1903, xv, 159

57 Morgan, H de Some Observations on the Micro organisms of Meat Poisoning and Their Allies Brit Med Jour, 1905, p 57

described by Morgan produce indol and are not agglutinated by Schottmueller's serum, therefore, they are not paratyphoid A bacilli, probably they are atypical forms of *Bacillus coli*

#### MORPHOLOGY AND CULTURAL CHARACTERISTICS OF PARATYPHOID A

The paratyphoid A is a short, actively motile bacillus, variable in size and morphologically indistinguishable from the typhoid bacillus. Its motility is more darting in character than the typhoid bacillus (Cushing, Gwyn, Schottmueller, Blumenthal, Coleman and Buxton, Hewlett, Allen, and Brion and Kayser). It has the same number (12 to 14), and distribution of flagella as the typhoid bacillus, sometimes long terminal flagella are observed (Cushing).

It stains readily. Bacilli taken from a growth on potato show polar staining (Schottmueller).

Para A grows best at a temperature of 37°C (Brion and Kayser). It is aerobic and facultative anaerobic. Exposure to a temperature of 60°C for a few minutes kills this bacillus, 55°C is not sufficient to destroy it (Cushing).

Bouillon is moderately clouded, not so much so as by *Bacillus coli communis* (Brion and Kayser).

Gelatin smear cultures develop a thin, blueish, glittering appearance, later the growth is thicker and porcelain white (Schottmueller), or the growth may have the same appearance as *Bacillus coli communis* (Brion and Kayser). Allen, Johnston, Hewlett and Blumenthal describe it as similar to the growth of the typhoid bacilli. At first the growth on the surface of gelatin consists of grape-leaf-form colonies which show no striations as the typhoid bacilli do (Schottmueller), pin-head-like colonies, 3 to 4 mm in diameter, appear after three or four days' growth, they are grayish and glistening, their surfaces are not striated, sometimes the center shows umbilication. The deeper colonies are ovoid and their outline is generally irregular (Brion and Kayser). Coleman and Buxton, Cushing, Hewlett, Allen, Johnston and Gwyn describe the growth of paratyphoid A on gelatin as indistinguishable from that of typhoid bacilli.

Milk is not coagulated by the bacillus (Allen, Blumenthal, Brion and Kayser, Coleman and Buxton, Cushing, Hewlett, Johnston, Schottmueller and Gwyn). Schottmueller observed, after several weeks' incubation, a slight transparency of milk. Milk is at first acidified, after a period of three weeks it becomes neutral and so remains, or becomes slightly alkaline. According to Hewlett, the amount of alkalinity is not sufficient to make the milk transparent.

Litmus whey according to Schottmueller, and Brion and Kayser, after forty-eight hours is turned rust-red, remains acid and does not become cloudy, Blumenthal, Coleman and Buxton observed a slight cloudiness of litmus whey, with reaction always acid

Allen and Gwyn experimented with litmus milk,<sup>58</sup> and observed slight acidifying during the first twelve hours, at the end of the first week the acidity started to decline and after ten days the litmus milk showed same reaction as control. Two weeks later they observed distinct alkalinity. This terminal alkalinity was observed, but only once, with cultures from one of Johnston's cases (Milefsky) and Cushing's case.

Agar smears show a very thin, grayish-white, transparent growth, indistinguishable from that of typhoid bacilli (all observers)

On Drigalski agar blue colonies, similar to typhoid, develop (Brion and Kayser and Blumenthal)

Neutral red agar containing grape sugar is fermented and becomes fluorescent (Schottmueller, Blumenthal and Brion and Kayser)

Grape sugar is fermented, with gas and acid production, also maltose and dextrose. Cane-sugar, milk-sugar and starch are not fermented (Schottmueller, Brion and Kayser, Allen, Cushing and Gwyn)

On potato there develops a barely visible moist, glistening growth (Blumenthal, Coleman and Buxton, Johnston and Schottmueller). Cushing describes the growth on potato as pale yellowish colored.

Indol production could not be detected by Schottmueller, Brion and Kayser, and Hewlett, Cushing, Allen and Johnston (in the case of Milefsky) observed slight indol formation.

The cultures of reported cases of paratyphoid A which we obtained from Král, of Piag, all show the same characteristics as our paratyphoid A cultures, Pittsburgh. The cultures obtained from Kial were the following cases Schottmueller's (cases of Barg and Muelle), Brion and

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58 Litmus milk is an undesirable medium to use for the study of the paratyphoid bacilli, and para A cannot be differentiated from other bacilli by its growth in litmus milk. When paratyphoid A bacilli are grown in milk, after a time the reaction of the medium becomes very variable. There is a possibility that during the time para A bacilli are being cultivated in milk, changes in the casein, independent of the presence of the para A bacilli, produce alkaline products which cause the terminal alkalinity and give rise to error, therefore, it is probable that the variations of the cultures of Allen's and Cushing's cases and one of Johnston's (Milefsky), observed when they were cultivated in litmus milk were only apparent and not real, the error being due to the use of an unreliable medium. Experiments made by us with cultures of bacteria from these same cases and most carefully prepared litmus whey all resulted the same, showing constant acid reaction and the litmus whey always clear, after weeks' incubation.

Kayser's, Coleman and Buxton's, Cushing's O, Hewlett's Case 7, Johnston's (of Milefsky and Badach), Gwyn's, Allen's (cases of Euster and Samuel) <sup>59</sup>

#### AGGLUTINATION TESTS MADE BY VARIOUS INVESTIGATORS

The results of agglutination tests made by the different authors who have reported cases of paratyphoid fever A are not comparable, because the technic used by them was rarely the same, and very few of their communications mention or explain the method pursued, serums of highly immunized animals was seldom used, and even the tests made with the patient's sera were not carried on to the titer limit in some cases. The following abstracts from the reports of cases contain practically all the information given by their authors concerning agglutination tests.

Gwyn isolated the bacillus from his patient's blood at different times during the course of the disease and the patient's serum agglutinated in a dilution of 1 200, which was the limit of the titer, this serum would not agglutinate typhoid bacilli, but agglutinated two colon bacillus cultures in a dilution of 1 50 and 1 60, however, these same colon bacillus cultures were also agglutinated by normal healthy serum in a higher dilution, 1 60 and 1 100.

Cushing<sup>60</sup> isolated from his patient a bacillus which he named O (which was a paratyphoid A bacillus), the patient's serum agglutinated it in a dilution of  $\frac{1}{2}$  to 2 in two hours. The serums of five healthy persons did not agglutinate the bacillus in a dilution of 1 10. A rabbit was immunized with hog-cholera bacilli, its serum agglutinated bacillus O and hog-cholera bacillus in a dilution of 1 5,000.

Bacilli taken from Schottmueller's two patients, Mueller and Baig, were not affected by the serum of a typhoid patient, both cultures were agglutinated equally in a dilution of 1 100 of serum taken from Mueller on the forty-third day of the disease. Serum taken from a paratyphoid B patient (Koecher) did not agglutinate the culture from either Mueller or Baig. The serum of another para B patient, Dr K., had no effect on either of the A cultures, but the sera of three other paratyphoid B patients,

59 Two cultures obtained from Longcope showed the same characteristics as the other para A cultures.

60 The results obtained by Cushing are remarkable in that we find it impossible to repeat them. A complete examination of this bacillus made with the greatest of care, and employing all the known means of identification, described in another part of this work, prove the organism isolated by Cushing, and named "bacillus O," to be a typical paratyphoid A bacillus, whereas his result would put it in the paratyphoid B group.

Krenzin, Thot and Seemann, caused group agglutination of both cultures, in the dilutions of 1 100, 1 50 and 1 100, respectively. Paratyphoid A serum taken from Mueller caused group agglutination of the para B, cultures taken from patients Krenzin, Thot and Seemann in a dilution of 1 100, the same serum also agglutinated *Bacillus coli* in the same dilution.

The serum taken from Hewlett's patient agglutinated the bacillus Noonan in a dilution of 1 100, but would not agglutinate the Eberth-Gaffky bacillus in a dilution of 1 10. The serum of a guinea-pig immunized with the bacillus Noonan agglutinated bacillus Noonan in a dilution of 1 5,000, also Gwyn's "paracolon," Schottmueller's A and one of Johnston's cases (Badach) in 1 5,000, Cushing's "O" and one of Johnston's cases (Milefsky) 1 500, and Coleman and Buxton's Case 7 1 100. It would not agglutinate Schottmueller's B, Kurth's para B, bacillus Strong, Eberth-Gaffky or *coli communis* in a dilution of 1 20.

The bacillus isolated from Brion and Kayser's patient was agglutinated by the patient's serum in a dilution of 1 1,000, this serum had no effect on the typhoid bacillus.

The serum from one of Johnston's cases (that of Milefsky) agglutinated bacillus Milefsky and bacillus Badach in a dilution of 1 50. This serum had no effect on the typhoid bacillus, *Bacillus cholerae suis*, *Bacillus enteritidis* or the colon bacillus.

Rolly's patient's serum agglutinated the isolated organism and other paratyphoid A cultures in a 1 500 dilution, and caused group agglutination of paratyphoid B bacillus in 1 250, also typhoid 1 50.

The bacilli taken from both Allen's patients, Samuel and Euster, were agglutinated in a dilution of 1 100 by serum taken from Samuel, Gwyn's and Johnston's cultures were agglutinated in 1 50, and typhoid bacillus 1 10 by the same serum. Euster's serum agglutinated his own bacillus in a 1 200 dilution, Samuel's 1 200, that of Gwyn's patient 1 50, that of both Johnston's 1 100 and typhoid bacillus 1 10.

#### VIRULENCE OF PARATYPHOID A BACILLUS

The virulence of the different A cultures was measured by the quantity of a 16-hour-old bouillon culture required to kill a white mouse in twenty-four hours, and the lethal doses were Gwyn's case, 0 2 c c, Coleman and Buxton's, 0 2 c c, Cushing's O, 0 2 c c, and case of Samuel, 0 2 c c, case of Badach, 0 3 c c, Brion and Kayser's case, 0 5 c c, and case of Euster, 0 5 c c.

## DESCRIPTION OF PARATYPHOID A BACILLUS, PITTSBURGH

This is a very motile short bacillus, with rounded ends, some thick others slender, occasionally occurring in chains. The average length of a stained specimen is 2.07 microns, being shorter than the *Bacillus coli*, which is 2 to 4 microns, and the Eberth-Gaffky bacillus, which averages 2.8 microns. The motility, especially of organisms recently taken from a patient's blood, is rapid and darting, in contrast to Eberth-Gaffky and the colon bacilli, which have an undulatory motion, and are much slower in motion. The activity is due to six or eight lateral flagella. Motility is greatest in bacilli fresh from a patient's blood, those taken from culture media are less motile, the motility decreases every day during their growth on artificial media. Positive microscopic differentiation of para A from Eberth-Gaffky bacilli is possible only occasionally in fresh specimens. The alkalinity and other unknown properties of culture media cause changes in the appearance of para A bacilli grown on them so that organisms cannot be distinguished from Eberth-Gaffky bacilli.

With the usual basic aniline dyes, in aqueous and alcoholic solutions, the para A bacillus does not stain deeply, but on the addition of an alkaline or phenol mordant the staining is deep. It is Gram-negative. All bacteria taken from gelatin and potato cultures show granular staining, this is occasionally observed in bacteria immediately after they have been isolated from the human body. All the bacilli of the typhoid-colic group stain the same way.

## GROWTH OF PARATYPHOID A BACILLI ON VARIOUS MEDIA

Para A bacilli grow best on slightly alkaline or neutral media at 37° C. They will grow without any change, but more slowly at temperatures down to 20° C., multiplying equally well under aerobic or anaerobic conditions.

After a few hours' growth in slightly alkaline bouillon there is a faint homogeneous clouding of the medium, just as occurs with the Eberth-Gaffky bacillus; a scanty flocculent sediment is precipitated. Scum formation occasionally develops in bouillon cultures cultivated for a long time, forty-eight cultures incubated for several months showed a scum on sixteen. Para B bacilli make bouillon more cloudy and cause a heavier precipitate, scum formation is about the same.

Litmus whey after ten hours' growth of para A bacilli is turned a deep red and remains red and clear permanently. Eberth-Gaffky bacilli cause the same change but in a less marked degree. Para B bacilli turn litmus whey red and cloudy in two or three days, about three weeks later it again turns blue and thereafter remains blue and cloudy.

Milk is unchanged by para A during first four or five months, remaining acid, after that time the reaction is variable, maybe slightly acid, amphoteric or alkaline. In eight or nine months the milk becomes clear, precipitates a granular sediment, turns orange-color and with the change in color becomes alkaline in reaction. After filtration, 100 c.c. are neutralized by 12 c.c. of decinormal sulphuric acid. Milk containing para B bacilli after incubation for fourteen to twenty days shows slight clearing without any precipitate, and when filtered 100 c.c. are neutralized by 10 c.c. decinormal sulphuric acid. The transparency of the milk caused by growth of para A and B bacilli seems to be due to a change in the casein. It is not due to saponification of the fat, a temperature of 37 C and the slight alkalinity are not sufficient to cause saponification. After many months' growth in milk eighty different cultures of typhoid bacilli were not affected in any way and showed no change.

In litmus milk-sugar, crystal-violet agar (Drigalski-Conrad), para A forms slightly elevated, round and oval colonies, some with regular and others with lobulated edges, bluish color and finely granular or smooth and sometimes lineated surface. The growth of para B and Eberth-Gaffky bacilli on this medium show same appearance as para A.

On Barsikow's nutrose sugar (grape and milk) litmus, para A acts as follows. One per cent nutrose milk-sugar litmus is turned red and remains clear, in 1 per cent nutrose grape-sugar litmus a raspberry-colored, flocculent precipitate falls to the bottom and the fluid remains clear. Para B bacilli produce the same changes in these media. Typhoid bacilli grow in them without causing any change, *Bacillus coli* coagulates both.

Indol formation either in bouillon or peptone water could not be detected by the extremely sensitive dimethylamidobenzaldehyde test.

On blood-agar the growth is like that of para B and typhoid bacilli, forty-eight hours after planting, dark green pin-head-sized colonies appear deep in the medium, on the surface there are linseed-sized colonies which are mouse-gray color.

Agar, slightly alkaline, smear cultures, after ten to fifteen hours, show a dull grayish-white surface, with cloudy condensations of moisture on the glass which cannot be distinguished from that formed by Eberth-Gaffky bacilli, para B show a thicker growth and more cloudy water of condensation.

Endo agar (fuchsin-sulphite agar) is not changed by the growth of para A bacilli which form colorless colonies as do para B and typhoid bacilli. On this medium *Bacillus coli communis* forms red colonies.

On malachite green agar para A forms small, round glassy, milk-cloudy colonies which are surrounded by a yellow ring, para B colonies have the same appearance, with the exception that the yellow ring which surrounds them is thicker and more marked. The growth of Eberth-Gaffky bacilli on this medium cannot be distinguished from that of para B bacillus, *Bacillus coli communis* rarely grows on this medium, occasionally a few atypical colonies which resemble the growth on para B are observed.

Neutral red agar containing 1 per cent grape sugar is fermented and changed to a yellowish fluorescence by both para A and B Typhoid bacilli cause the same change, but in a less marked degree. Para B bacilli turn litmus whey red and cloudy in two or three days, about three weeks later it turns blue and thereafter remains blue and cloudy.

On gelatin plates three or four days after planting, round and oval colonies appear, they have sharp edges, are 20 to 30 microns in diameter and have an uniformly granular surface, the growth of the para B bacillus on this medium is just the same.

Gelatin slant tubes of para A after ten or twelve days show a thin transparent, dull white film, just like the Eberth-Gaffky. Para B forms a thick wedge-shaped growth with the base of the wedge at the bottom of the tube, it looks like porcelain.

Gelatin stab cultures of para A in ten or fifteen days develop a dull white growth around the stab, which looks like a cylindrical brush made up of fine closely set bristles of slightly irregular lengths. Gelatin stab cultures of para A cannot be distinguished from those of para B and typhoid Colon bacilli liquefy gelatin (See Photos Nos 1-4).

On potato para A forms an invisible growth like the Eberth-Gaffky bacillus, and the growth is not affected by either acidity or alkalinity. Para B forms a thick yellowish-brown growth like *Bacillus coli communis*. Conrad, Juergens, Drigalski and Korte state that the growth of para A on potato is either invisible or only slightly visible. Schottmueller and Bruck describe it as being similar to the growth of the *Bacillus coli*. Possibly the difference in these observations is due to variations in the different organisms cultivated.

On lactose and glucose *Bacilli coli communis* produce strong acidity, para A and typhoid bacilli much less. Para A and Eberth-Gaffky bacilli form about the same amount of acid on glucose, on lactose they form the same amount during the first two days, after that the typhoid bacilli cause less acidity than the para A, probably because of the development of an alkaline substance by the typhoid bacilli.

FERMENTATION OF CARBOHYDRATES AND ALCOHOLS BY PARATYPHOID A  
BACILLI

Typhoid, paratyphoid and colon bacilli can be differentiated by their growth on carbohydrates and alcohols, but para A cannot be distinguished from paratyphoid B. The typhoid (Eberth-Gaffky) bacillus does not ferment any of the carbohydrates or alcohols. *Bacillus coli communis* ferments all the carbohydrates except raffinose, amylose and inulin.

The disaccharids, lactose and saccharose are not fermented by either para A or B, maltose is not fermented by para A, but some cultures of para B cause slight fermentation.

Raffinose is not fermented by either para A or para B.

Arabinose is fermented by all the para A and B bacilli, except para A Pittsburgh numbers 163 and 164 and para B Longcope and Philadelphia.

Xylose is fermented by very few cultures of A and B, most of them cause no fermentation.

Of the hexose group, considerable fermentation of *d*-glucose and *d*-fructose is caused by all the para A and B bacilli. Only a few cultures ferment *d*-mannose and *d*-galactose, and but little gas is formed.

The polysaccharids, amylose and inulin are not fermented. Dextrose is strongly fermented by all the cultures of para A and B.

The three-hydroxy (triaxonic) alcohol, glycerin and the four-hydroxy (tetraxonic) alcohol, erythritol, are not fermented by either para A or B. Of the six-hydroxy (hexa-axonic) group, mannitol is strongly fermented by all, isodulcitol is weakly fermented by all, and dulcitol is slightly fermented by 12 per cent of the cultures.

The gases liberated by these fermentations are hydrogen and carbonic acid, in proportions varying from 1:1 to 1:3. After oxidation of the hydrogen and the absorption of the carbonic acid, a slight residue of gas remains.

We believe that this residue is either nitrogen or methane. After fermentation the bouillon is strongly acid.

#### TECHNIC

All the carbohydrates and alcohols used in these experiments were of the highest chemical purity, they were obtained from Kahlbaum of Berlin.

The preparation of the media was as follows. A quantity of bouillon sufficient for all tests was made. It was then fermented with yeast for twenty-four hours, at the end of that time sufficient calcium carbonate was added to neutralize the acidity and precipitate the yeast, after which it was boiled for one hour, then drawn through a thick, compact, paper-pulp filter by a suction pump. The resultant clear, plain, bouillon was then inoculated with all the different cultures of para A and B bacilli and incubated at 37°C for twenty-four hours, if at the end of that time no fermentation occurred the different carbohydrates and alcohols were added and results observed.

This preliminary testing of the bouillon before adding the carbohydrates and alcohols is essential, because experiments with different samples of plain bouillon have shown that some of them contain a substance fermented by paratyphoid bacilli. What the fermentable substance is we do not know, but do not believe it is glycogen, because muscle sugar disappears shortly after an animal dies, and the means from which the bouillons are made had been in the refrigerator for several weeks. Escherich and Pfaundler have studied this fact for several years and state that the substance in plain bouillon, which ferments, is grape-sugar, our experiments seem to disprove this. Whatever the substance is, we know that it occurs in some, but not in all samples of plain bouillon, that it is fermented by yeast and paratyphoid bacilli, that its presence in some of the bouillon used for experiments with paratyphoid bacilli by various investigators has been the cause of discrepancies in their findings, that it can be entirely removed from bouillon by fermentation with yeast, and that such preliminary fermentation will exclude the probability of misleading and erroneous results.

#### ACID PRODUCTION BY GROWTH ON SUGAR

Quantitative and qualitative tests of acid which result from the growth of paratyphoid A, Eberth-Gaffky, and coli bacilli were made, the technic as follows:

To slightly alkaline bouillon 4 per cent of grape or milk sugar was added, the alkalinity of the bouillon estimated by titration with hundredth normal sulphuric acid. The acidity of the bouillon, after the growth of bacteria in it, was estimated by titration with hundredth normal sodium hydroxid solution, using phenolphthalein as indicator. Our results are shown in Table 4.

TABLE 4.—ACIDITY OF BOUILLON AFTER GROWTH OF BACTERIA  
STERILE BOUILLON, WITH 4 PER CENT GRAPE SUGAR ADDED, ALKALINITY ESTIMATED BY  
TITRATION WITH 16 C C CENTINORMAL SULPHURIC ACID, WITH 4 PER CENT  
MILK-SUGAR, ALKALINITY ESTIMATED BY TITRATION WITH 15 5 C C CENTI-  
NORMAL SULPHURIC ACID, ACIDITY AFTER GROWTH OF BACTERIA  
ESTIMATED BY TITRATION WITH CENTINORMAL POTASSIUM  
HYDROXID, PHENOLPHTHALEIN AS INDICATOR

	Coli B Grape S	Coli B Milk-S	Para A Grape S	Para A Milk-S	Typhoid Grape S	Typhoid Milk-S
7/30	64 6	57 4	54 0	32 6	53 4	37 6
7/31	66 4	55 0	57 0	29 2	58 6	25 0
S/ 1	66 0	52 8	62 4	28 0	61 4	15 0
S/ 2	65 8	57 0	64 6	25 0	58 2	8 0
S/ 3	68 0	60 0	61 0	24 8	59 6	7 8
S/ 4	65 8	57 6	60 0	26 2	59 2	5 2
S/ 5	69 6	59 0	64 0	21 0	54 2	5 4
S/ 6	67 0	61 2	63 0	17 0	58 0	4 8
S/ 7	69 0	62 2	61 8	13 0	62 4	5 6

So few cases of paratyphoid A have been reported that it is impossible to say at this time whether it can be differentiated culturally from para B. There is no characteristic difference in the growth of para A and para B on agar, Drigalski-agar (Figs 5 to 8), endo-agar, methyl-green agar, neutral-red agar, potato, nutrose-lactose-litmus or nutrose-grape-sugar-litmus. In bouillon the paratyphoid A bacillus generally

causes slight cloudiness, but the difference is too slight to be a distinguished factor, both cause the same scum formation

There is no marked difference in the fermentation of the various carbohydrates and alcohols, the slight variations being quantitative, not qualitative. The only cultural differences are shown in milk and litmus whey. Milk containing paratyphoid A is unchanged after standing for five months, while milk containing paratyphoid B bacilli becomes transparent in two or three weeks. Litmus whey containing para A remains constantly red and perfectly clear, litmus whey containing para B soon becomes cloudy and continues so, at first it is red, later it is blue.

#### RESISTANCE OF PARATYPHOID A AND B BACILLI TO TEMPERATURE

Paratyphoid A bacilli in milk and in bouillon are killed by a temperature of 70 C in fifteen minutes. They will live indefinite time, more than a year, in milk which was sterile when they were put in it, and retain all their vigor, virulence and characteristics. In milk and water containing saprophytic organisms, paratyphoid bacilli A and B are destroyed in a few weeks. After standing in an absolutely dry jar for six months, the paratyphoid A bacilli were found to be alive and unchanged. Paratyphoid B withstand higher temperatures than para A bacilli B. Fischer, also Vagedes found that a temperature of 60 maintained for half an hour did not always kill para B bacilli, and after exposure to a temperature of 70 C from ten to twenty-five minutes and 75 C for five minutes, there always remained some living germs. Kolle states that paratyphoid B bacilli in milk are all killed by a temperature of 60 C maintained for fifteen minutes. We found, after heating six different cultures of paratyphoid B to 60 C for half an hour, that four of them had been killed, the two cultures which withstood 60 C for half an hour were destroyed by that temperature maintained for one hour.

#### VIRULENCE OF PARATYPHOID A BACILLI

Paratyphoid A bacilli are much less virulent than para B bacilli, 0.3 cc of a twenty-four-hour-old bouillon culture injected into the peritoneal cavity of a mouse will kill it in one day. In proportion to their body weight, guinea-pigs and rabbits are more susceptible than mice. A 250 gram guinea-pig will die forty-eight hours after receiving, intraperitoneally, 0.5 cc of a twenty-four-hour-old bouillon culture of para A bacilli. Intravenous injections of 0.5 cc of a twenty-four-hour-old bouillon culture of para A bacilli kill 1,500 gram rabbits in twenty-four hours.

Animals inoculated with paratyphoid bacilli show the clinical course and post-mortem changes of septicemia, after death pure cultures of the bacteria can be isolated from their blood and internal organs

Mice and guinea-pigs fed for months on nothing but bread and meat, grossly infected with para A bacilli, did not become ill or die, and examination of their intestinal contents showed no para A bacilli

#### TOXIN FORMATION

Attempts to isolate a toxin formed by para A bacilli were unsuccessful Bouillon cultures were incubated at 37° for one, three, five, ten, twenty and thirty days, then filtered through a Pasteur-Chamberland filter and the filtrate injected intraperitoneally and intravenously into mice, guinea-pigs and rabbits, the doses ranging from 1 to 10 cc

Two rabbits which weighed 2,000 grams each received intravenous injections of 5 cc of the filtrate, three times in eight days, the only symptom they showed was progressive emaciation, and four weeks after last injection they died, post mortem the internal organs showed no change

When growing in bouillon paratyphoid A bacilli form a scum on the surface We cultivated them over large surfaces of bouillon where there was free access of oxygen, also under anaerobic conditions, in different degrees of alkalinity, upon the various carbohydrates and different serum, but in no case could a toxin be obtained The para A bacilli were planted on large agar plates and incubated at 37° C for twenty-four hours, at the end of that time some were washed off with sterile water, others with normal salt solutions, the fluids were then agitated for twenty-four hours at 37° C , after that they were filtered and the filtrate was injected into mice, guinea-pigs and rabbits, but produced no ill effect

In the serums of all these animals, four weeks after inoculation, we found agglutinins and bacteriolysins, but no antitoxin The serums from these animals were refrigerated for three or four weeks, at the end of that time they had lost their bacteriolytic power, then the fluid was injected into two groups of animals The first group were injected with the serums and, at the same time, inoculated with fresh cultures of paratyphoid A bacilli, those of the second group were injected with the serums only, twenty-four hours later, they were injected with the same as the first group Control animals were injected with nothing but the bacteria They all died in the same way and at the same time

These experiments show that the paratyphoid A bacilli does not form extra-cellular toxins, that toxemia is caused by endotoxins liberated when bacilli disintegrate, and our investigations of the other paratyphoid bacilli

lead us to believe that the same is true of the paratyphoid B bacilli Uhlenhuth<sup>61</sup> has found in filtrates from fourteen-day-old bouillon cultures of para B bacilli toxic substance to mice and guinea-pigs Kutscher and Meinike,<sup>62</sup> Conradi, Drigalski and Juegens<sup>11</sup> always get negative results, they have not been able to obtain heat-proof toxins Rolly<sup>63</sup> and Kutscher<sup>35</sup> isolated heat-proof toxins from their paratyphoid B bacilli cultures

The different results obtained by the above-mentioned observers seem to be due to the differences in the bacteria The toxicity of the paratyphoid B bacilli varies greatly Aionsohn some time ago obtained typhoid toxin (Eberth-Gaffky) bacilli, which is a stable endotoxin, but which does not produce a true antitoxin in animals

Our experiments and observations are in accord with those of the majority of workers in this field and show that the paratyphoid B bacilli are usually less toxic than the Eberth-Gaffky bacilli, and that paratyphoid A bacilli are always less toxic than either typhoid or paratyphoid B bacilli

#### AGGLUTINATION

Between the second and third day of the disease is the earliest time agglutination has been observed, it is positive in 50 per cent of all cases of typhoid fever by the eighth day, in 84 per cent by the fifteenth day, and 95 per cent by the twenty-second day

Bünn and Kayser say that the agglutinations are present early and through the entire course of the disease in the great majority of cases In exceptional cases the serum never shows this property at any time during the illness, therefore a constantly negative result does not exclude the diagnosis of typhoid fever

In most cases the highest titer is reached early in convalescence, after which it gradually declines Occasionally the highest titer is observed during the disease, and may rapidly fall or disappear at any time during the illness The patient's serum may retain the power to agglutinate for months or years after recovery has been complete Lentz<sup>65</sup> observed its presence in a dilution of 1:50 in two women seven and one-half and

61 Uhlenhuth Zur Kenntniss der gastrointestinalen Fleischvergiftungen und den biologischen Eigenschaften ihrer Erreger von Leuthold Gedenkschi, 1906, p 71

62 Kutscher and Meinike Vergleichende Untersuchungen über Paratyphusbakterien und ihre immunologischen Beziehungen Ztschr f Hyg u Infektionskrankh, 1906, p 301

63 Rolly Ueber eine Massenvergiftungs Epidemie mit Bohnengemuse Munchen med Wehnschr, 1906, p 1798

65 Lentz Immunität bei Typus In Kolle and Wassermann's Handbuch der pathogenen Micro Organismen, IV, 849

eleven years after recovery from typhoid fever. In typhoid fever the titer of the patient's serum is usually between 1:40 and 1:300, it may go up to 1:1,000 or 1:2,000. Foerster<sup>66</sup> and Juergens<sup>67</sup> have seen titers of from 1:5,000 to 1:50,000, but their observations were made microscopically with a high power oil immersion lens.

The fact that the serum of normal healthy people who have never been ill occasionally agglutinate bacteria, and more important, that the serum of one suffering with typhoid fever occasionally has in addition to its power of agglutinating the Eberth-Gaffky bacillus an equally strong or stronger power to agglutinate other bacilli, lessens the value of this test as a means of diagnosis and has excited much controversy concerning the specific nature of this test. The serum of a patient affected with any of the organisms belonging to the typhoid coli group, Eberth-Gaffky bacillus, paratyphoid A and B, *Bacillus psittacosis*, *Bacillus enteritidis* (Gartner), hog-cholera bacillus, the various bacilli which cause meat-poisonings, paracolon bacillus and *Bacillus coli communis*, may show the phenomena of group agglutination. Thus the serum of the patient ill as a result of meat-poisoning, not infected with typhoid bacilli, may agglutinate the bacillus responsible for the disease, and at the same time have the power to agglutinate typhoid bacilli in a lesser, equal or greater degree. This has been observed by Huehneimann, Conradi, Drigalski, Juergens and many others, Zupnik<sup>68</sup> maintains that agglutination is only a group reaction and of no value in distinguishing the different members of the group. Lentz, Drigalski and Fischer believe that this double agglutination is such a rare occurrence that it does not impair the value of the agglutination test in making a diagnosis.

Castellani<sup>69</sup> described a method by which the organism causing a disease could be identified when the patient's serum showed group agglutination and agglutinated two or more bacteria. According to his theory serums which possess the property of group agglutination contain a principal and auxiliary agglutinins. The principal agglutinin is the one formed by the organism causing the disease and is identified by its superior power of agglutination over the auxiliary agglutinins. This

<sup>66</sup> Foerster, O. Quantitative Untersuchungen über die agglutinirende und baktericide Wirkung des Blutserums von Typhuskranken und Rekonvaleszenten. *Ztschr f Hyg u Infectionskrankh*, 1897, No. 3.

<sup>67</sup> Juergens, G. Beobachtungen über die Widal'sche Reaction und die Mitagglutination der Typhusbacillen. *Ztschr f Hyg u Infectionskrankh*, 1903, p. 372.

<sup>68</sup> Zupnik, L. Ueber Gattungs spezifische Immunitätsreactionen. *Ztschr f Hyg u Infectionskrankh*, 1904, p. 447.

<sup>69</sup> Castellani, A. Die Agglutination bei gemischter Infektion und die Diagnose der letzteren. *Ztschr f Hyg u Infectionskrankh*, 1902, p. 1.

theory has been proved wrong by a great mass of evidence produced by many experimenters, consequently the test is valueless

Castellani's method is to take a serum which agglutinates two different bacteria, add to it one of the bacteria until its power to agglutinate that organism is exhausted, then by centrifugation separate the agglutinated bacilli from the serum, add the other bacteria until the titer is exhausted. The organism for which the serum possesses the greatest power of agglutination is the causing organism. Castellani failed to discover the all-important fact that when you extract from a group agglutination serum the power to agglutinate one bacillus, you thereby increase its power to agglutinate the other.

Authorities disagree as to the lowest dilution of a patient's serum which is of value in making an agglutination test for the diagnosis of typhoid fevers, Widal says 1 10, Ziemke 1 20, Stern and Kolle 1 30, Gruenbaum 1 32, Skowler and Foerster 1 40, Fraenkel and Kohler 1 50, Bruns and Kayser 1 75

Kassel and Mann have shown that occasionally the sera of patients ill with croupous pneumonia will agglutinate typhoid bacilli in a dilution of 1 40. Van Ordt has found that the serum of a patient with suppurative meningitis will do the same thing. Many investigators state that the serums of most patients suffering with jaundice will agglutinate typhoid bacilli. Eckhardt<sup>70</sup> has observed this in a dilution of 1 100, Gruenbaum<sup>71</sup> and Koehler 1 40<sup>72</sup>.

A study of many thousand cases of typhoid fever, for each of which an agglutination with the patient's serum was made, shows that a diagnosis of typhoid fever by an agglutination test made with the patient's serum will be correct in 60 per cent of all cases. In 40 per cent agglutination tests made with the patient's serum will not lead to the correct diagnosis. This is true for all the diseases caused by members of the typhoid group.

Since it is important to have an absolutely reliable method of making an early diagnosis of typhoid fever, it is most desirable that we use an improved technic that eliminates the probability of error from the results of agglutination tests. Many hundred agglutination and group agglutination tests made by titrating the serum of highly immunized animals

70 Eckhart Widal'sche Serum Reaction bei Weil'scher Krankheit Munchen med Wehnschr, 1902, No 27

71 Grunbaum, M S Ueber den Gebrauch der agglutinirenden Wirkungen von menschlichen Serum fur die Diagnose des Abdominal-Typhus Munchen med Wehnschr, 1897, No 13, p 330

72 Koehler, F Das Agglutinationsphanomen, Klinische u Experimentelle Studien Klinisches Jahrbuch, 1901, viii, 39

against the bacilli taken from the patient's blood and observing the result macroscopically and with only low-power microscope, show this to be the method which meets all requirements.

#### HIGH AGGLUTINATION SERUMS

Zupnik's<sup>68</sup> statement that agglutination of laboratory cultures of bacilli with patient's serum is only a group reaction, does not apply to the agglutination of bacilli taken from a patient and agglutinated with the serum of a highly immunized animal. The serum of highly immunized animals may show the phenomena of group agglutination, but when this is present it is so weak that it never makes the result doubtful, the highest group agglutination, in proportion to the principal agglutinin, was observed and recorded by Juergens, in low titer serums, and the group agglutination was only for the two nearest relations in the typhoid coli group. He observed a typhoid serum with a titer of 1 500 for typhoid bacilli which agglutinated paratyphoid bacilli in a dilution of 1 200, and a paratyphoid serum with a titer of 1 400 for paratyphoid bacilli which agglutinated typhoid bacilli in a dilution of 1 200, even in these extraordinary cases the difference is so great that error need not be made. The serum of animals which have been highly immunized will agglutinate the bacillus with which the immunity was produced in a dilution of from 1 500 to 1 50,000. The higher the dilution which will agglutinate the bacillus producing the immunity, the lower in proportion the power of group agglutination.

When the same technic is used and all precautions taken to obtain uniform results in highly immunizing animals against typhoid disease, there will still be variations in the power of the serums of the different animals to agglutinate cultures of the bacillus with which the immunity was produced. Thus we take a pure culture of Eberth-Gaffky bacilli, immunize with it twelve guinea-pigs having the same weight, the highest dilutions in which the serums of these pigs will agglutinate the cultures of Eberth-Gaffky bacilli used to produce the immunity are as follows: One 1 800, one 1 2,000, one 1 5,000, two 1 20,000, three 1 30,000, two 1 40,000, one 1 50,000 and one 1 60,000. These variations are due to differences in the animals, and do not result from faulty technic; nor are some of them weaker than others, because the power of agglutination is unstable and partly lost after removal from the animal body, as Hetsch believes.

After an animal has been immunized its serum should be titrated against the culture with which the immunity was produced, several times daily on three or four consecutive days to establish the limit of its titer.

Only serums that show a titer of 1 10,000 or higher should be used, because only with serums possessing such high power of agglutination can a differential diagnosis be made between the numerous members of typhoid-coli group. For the result of an agglutination test to be acceptable as absolutely diagnostic the bacilli taken from the patient must be agglutinated by the animal serum in nearly as high a dilution as the bacilli used in immunizing the animal. The fact that such a test can be substituted for Pfeiffer's bacteriolytic test, giving reliable results and being less difficult to perform and requiring less time, greatly enhances the value of an agglutination test made with the serum of a strongly immunized animal.

When a test is made with bacteria taken directly from the patient's blood and the result is negative, that is not proof that the patient has not the disease. In such a case it is necessary to take some bacilli from the blood, incubate them at 37 C on artificial culture media for three days and titrate the animal serum against them, because certain conditions of the human body cause variations in the bacilli which makes their agglutination more difficult or impossible, and when the bacilli are replanted in artificial culture media and incubated for several days they regain their normal properties and are uniformly agglutinable. Virulent cultures are harder to agglutinate than avirulent cultures, very motile bacilli are more difficult to agglutinate than slightly motile bacilli, when typhoid bacilli are growing in a temperature of 42 C they cannot be agglutinated, but if the temperature is reduced to 37 C after several days they are again agglutinable, occasionally, of a number of typhoid bacilli taken from one individual, some will be difficult to agglutinate and others will be easy to agglutinate.

#### AGGLUTINATION TEST TECHNIC

The serum used in making these tests was obtained from rabbits that had been immunized with cultures of typhoid (Eberth-Gaffky), paratyphoid B (Schotmueller), and paratyphoid A ("Pgh") bacilli. Immunization was produced by intravenous injections of bacilli that had been killed by exposure to a temperature of 60 C. The first injection was 0.5 c.c. of a twenty-four-hour-old bouillon culture, seven days later an eighteen-hour agar culture was washed with 5 c.c. of normal salt solution and 1 c.c. of that solution was injected, similar injections were given on the fourteenth and twenty-first days, and five weeks after the first injection had been given the titer of each serum was estimated and only those serums which showed a titer limit of 1 40,000 were used.

Kutscher and Meinike<sup>73</sup> have observed that immunization by small amounts of living bacilli, as practiced by Friedberger, does not develop a strong power of agglutination in the serum. After using both methods extensively we believe the best results are obtained by producing immunity with injections of large numbers of dead bacteria. Each serum, on three consecutive days, was titrated against its own bacillus, at the same time tests were made with normal rabbits' serums against the different cultures, in dilutions from 1:10 to 1:100.

The agglutination tests were made by Proescher's<sup>74</sup> method, which is as follows. Twelve test-tubes, each containing 1 cc of sterile normal salt solution, are put in a row. To the first is added 1 cc of a 1:10 dilution of the serum, the tube is then shaken so as to mix its contents thoroughly. Tube No. 1 now contains 2 cc of a 1:20 dilution of the serum, 1 cc of the contents of No. 1 are transferred to No. 2, after which No. 1 contains 1 cc of a 1:20 dilution of serum, and No. 2 contains 2 cc of a 1:40 dilution. One cc of the contents of No. 2 are then transferred to No. 3, this transfer is continued to the eleventh tube, the 1 cc removed from No. 11 is discarded. No serum is put in No. 12, it is used as a control. Now there is 1 cc of fluid in each of the twelve tubes. From the first to the eleventh, inclusive, they contain increasingly higher dilutions of the serum as follows: 1:20, 1:40, 1:80, 1:160, 1:320, 1:640, 1:1,280, 1:2,560, 1:5,120, 1:10,240, and 1:20,480. The twelfth tube contains 1 cc of sterile normal salt solution.

The next step is to add 1 cc of an emulsion of the bacilli to each tube, now every tube contains 2 cc of fluid and the dilution of the serum in each tube has been doubled, so that the first tube now contains 2 cc of a 1:40 dilution of serum plus the bacilli, and the eleventh tube 2 cc of a 1:40,960 dilution plus bacilli. The twelfth tube (control) contains 2 cc of an emulsion of bacilli in normal salt solution.

The contents of the twelve tubes are emptied into twelve square glass dishes, these dishes are piled one upon the other and the top one covered with a piece of glass. They are then incubated at 37°C for six hours, at the end of that time they are removed from the incubator and examined.

<sup>73</sup> Kutscher and Meinike Vergleichende Untersuchungen über Paratyphus, Enteritis und Mausetyphusbakterien und ihre immunologischen Beziehungen Ztschr f Hyg u Infektionskrankh 1906, p 301.

<sup>74</sup> Proescher, F. Zur Anstellung der Widal'schen Reaction Centrálbl f Bakteriol, XXXI, 400.

\*The emulsion of the bacilli used for this purpose is obtained in the following way. A sixteen-hour-old agar culture of the bacteria is washed with 10 cc of normal salt solution. The salt solution is then shaken until the bacteria are thoroughly distributed through it and do not show any collection in groups when examined microscopically.

Beginning with the twelfth they are examined in order to the first. They are inspected macroscopically, then microscopically, with a low power lens and with the reflector of the microscope so arranged as to give the greatest amount of diffusion to the rays of light. In the lowest dilution large irregular clumps are observed, the higher the dilution the smaller and less compact are the clumps.

By this method, after some experience and observance of controls, the agglutination can be observed to the limit of the titer. Errors from pseudo-agglutination are precluded, and the variation between the results of repeated experiments are very much less than by any other method, which proves this the most exact and reliable method.

It is the consensus of opinion of investigators that observation of agglutination with an oil-immersion lens is uncertain and often misleading, that the most reliable observations are those made microscopically, or with a low-power lens, and that the latter method should be used, especially when comparison is desirable. Comparison of the results of different experiments can be of value only when the same technic has been used for all.

For comparative investigations it is important to know that the same bacillus grown on different agars varies in its susceptibility to agglutination. We often find in preliminary tests the controls spontaneously agglutinated. We made several different lots of agar on different days and planted paratyphoid bacilli on each. Later the agglutination of the bacteria from each of the agars was tried and the agar from which the bacilli were taken that gave the best results was employed exclusively for the growth of all bacteria used in making agglutination tests.

Why different agars vary in their effects on bacilli is not known. Kutscher and Meinke believe that this phenomenon is due to differences in alkalinity. We experimented with agars of different degrees of alkalinity, and whether the alkalinity was strong or slight made no difference in the effect upon the bacteria. It is probable that the meat and peptone are responsible for the lack of uniformity. Different lots of agar made with the same meat and with different samples of peptone gave different results, other lots of agar made with the same meat and same peptone gave uniform results.

#### AGGLUTINATION OF PARA A CULTURES, PITTSBURGH

The serum used to agglutinate the para A, culture Pgh, was obtained from a rabbit which had been highly immunized with para A No 65, Pgh, this had a titer of 1 50,000 (See Table 5.)

It will be seen that the majority of the Pgh cultures (39) were agglutinated to the titer limit by one Pgh serum, 8 were agglutinated to

TABLE 5—PARA A CULTURES PITTSBURGH, AGGLUTINATED WITH PARA A SERUM PITTSBURGH  
(Titer 1 50,000)

TABLE 6—PARA A CULTURES PITTSBURGH, AGGLUTINATED WITH PARA A SERUM SCHOTTMUELLER (CASE BARG)

Culture No.	Dilution	40	80	160	320	640	1280	2560	5120	10240	20480	40960
4	5	9	10	13	14	16	20	27	32	33	35	39
5	10	29	32	33	35	39	46	52	53	57	60	61
6	11	32	33	35	37	39	46	52	53	57	60	61
7	12	32	33	35	37	39	46	52	53	57	60	61
8	13	32	33	35	37	39	46	52	53	57	60	61
9	14	32	33	35	37	39	46	52	53	57	60	61
10	15	32	33	35	37	39	46	52	53	57	60	61
11	16	32	33	35	37	39	46	52	53	57	60	61
12	17	32	33	35	37	39	46	52	53	57	60	61
13	18	32	33	35	37	39	46	52	53	57	60	61
14	19	32	33	35	37	39	46	52	53	57	60	61
15	20	32	33	35	37	39	46	52	53	57	60	61
16	21	32	33	35	37	39	46	52	53	57	60	61
17	22	32	33	35	37	39	46	52	53	57	60	61
18	23	32	33	35	37	39	46	52	53	57	60	61
19	24	32	33	35	37	39	46	52	53	57	60	61
20	25	32	33	35	37	39	46	52	53	57	60	61
21	26	32	33	35	37	39	46	52	53	57	60	61
22	27	32	33	35	37	39	46	52	53	57	60	61
23	28	32	33	35	37	39	46	52	53	57	60	61
24	29	32	33	35	37	39	46	52	53	57	60	61
25	30	32	33	35	37	39	46	52	53	57	60	61
26	31	32	33	35	37	39	46	52	53	57	60	61
27	32	33	35	37	39	46	52	53	57	60	61	62
28	33	35	37	39	46	52	53	57	60	61	62	63
29	34	36	38	40	48	54	62	69	73	77	81	83
30	35	37	39	41	49	55	63	70	74	78	82	84
31	36	38	40	42	50	56	64	71	75	79	83	85
32	37	39	41	43	51	57	65	72	76	80	84	86
33	38	40	42	44	52	58	66	73	77	81	85	87
34	39	41	43	45	53	59	67	74	78	82	86	88
35	40	42	44	46	54	60	68	75	79	83	87	89
36	41	43	45	47	55	61	69	76	80	84	88	90
37	42	44	46	48	56	62	70	77	81	85	89	91
38	43	45	47	49	57	63	71	78	82	86	90	92
39	44	46	48	50	58	64	72	79	83	87	91	93
40	45	47	49	51	59	65	73	80	84	88	92	94
41	46	48	50	52	60	66	74	81	85	89	93	95
42	47	49	51	53	61	67	75	82	86	90	94	96
43	48	50	52	54	62	68	76	83	87	91	95	97
44	49	51	53	55	63	69	77	84	88	92	96	98
45	50	52	54	56	64	70	78	85	89	93	97	99
46	51	53	55	57	65	71	79	86	90	94	98	100
47	52	54	56	58	66	72	80	87	91	95	99	101
48	53	55	57	59	67	73	81	88	92	96	100	102
49	54	56	58	60	68	74	82	89	93	97	101	103
50	55	57	59	61	69	75	83	90	94	98	102	104
51	56	58	60	62	70	76	84	91	95	99	103	105
52	57	59	61	63	71	77	85	92	96	100	104	106
53	58	60	62	64	72	78	86	93	97	101	105	107
54	59	61	63	65	73	79	87	94	98	102	106	108
55	60	62	64	66	74	80	88	95	99	103	107	109
56	61	63	65	67	75	81	89	96	100	104	108	110
57	62	64	66	68	76	82	90	97	101	105	109	111
58	63	65	67	69	77	83	91	98	102	106	110	112
59	64	66	68	70	78	84	92	99	103	107	111	113
60	65	67	69	71	79	85	93	100	104	108	112	114
61	66	68	70	72	80	86	94	101	105	109	113	115
62	67	69	71	73	81	87	95	102	106	110	114	116
63	68	70	72	74	82	88	96	103	107	111	115	117
64	69	71	73	75	83	89	97	104	108	112	116	118
65	70	72	74	76	84	90	98	105	109	113	117	119
66	71	73	75	77	85	91	99	106	110	114	118	120
67	72	74	76	78	86	92	100	107	111	115	119	121
68	73	75	77	79	87	93	101	108	112	116	120	122
69	74	76	78	80	88	94	102	109	113	117	121	123
70	75	77	79	81	89	95	103	110	114	118	122	124
71	76	78	80	82	90	96	104	111	115	119	123	125
72	77	79	81	83	91	97	105	112	116	120	124	126
73	78	80	82	84	92	98	106	113	117	121	125	127
74	79	81	83	85	93	99	107	114	118	122	126	128
75	80	82	84	86	94	100	108	115	119	123	127	129
76	81	83	85	87	95	101	109	116	120	124	128	130
77	82	84	86	88	96	102	110	117	121	125	129	131
78	83	85	87	89	97	103	111	118	122	126	130	132
79	84	86	88	90	98	104	112	119	123	127	131	133
80	85	87	89	91	99	105	113	120	124	128	132	134
81	86	88	90	92	100	106	114	121	125	129	133	135
82	87	89	91	93	101	107	115	122	126	130	134	136
83	88	90	92	94	102	108	116	123	127	131	135	137
84	89	91	93	95	103	109	117	124	128	132	136	138
85	90	92	94	96	104	110	118	125	129	133	137	139
86	91	93	95	97	105	111	119	126	130	134	138	140
87	92	94	96	98	106	112	119	127	131	135	139	141
88	93	95	97	99	107	113	120	128	132	136	140	142
89	94	96	98	100	108	114	121	129	133	137	141	143
90	95	97	99	101	109	115	122	130	134	138	142	144
91	96	98	100	102	110	116	123	131	135	139	143	145
92	97	99	101	103	111	117	124	132	136	140	144	146
93	98	100	102	104	112	118	125	133	137	141	145	147
94	99	101	103	105	113	119	126	134	138	142	146	148
95	100	102	104	106	114	120	127	135	139	143	147	149
96	101	103	105	107	115	121	128	136	140	144	148	150
97	102	104	106	108	116	122	129	137	141	145	149	151
98	103	105	107	109	117	123	130	138	142	146	150	152
99	104	106	108	110	118	124	131	139	143	147	151	153
100	105	107	109	111	119	125	132	140	144	148	152	154
101	106	108	110	112	120	126	133	141	145	149	153	155
102	107	109	111	113	121	127	134	142	146	150	154	156
103	108	110	112	114	122	128	135	143	147	151	155	157
104	109	111	113	115	123	129	136	144	148	152	156	158
105	110	112	114	116	124	130	137	145	149	153	157	159
106	111	113	115	117	125	131	138	146	150	154	158	160
107	112	114	116	118	126	132	139	147	151	155	159	161
108	113	115	117	119	127	133	140	148	152	156	160	162
109	114	116	118	120	128	134	141	149	153	157	161	163
110	115	117	119	121	129	135	142	150	154	158	162	164
111	116	118	120	122	130	136	143	151	155	159	163	165
112	117	119	121	123	131	137	144	152	156	160	164	166
113	118	120	122	124	132	138	145	153	157	161	165	167
114	119	121	123	125	133	139	146	154	158	162	166	168
115	120	122	124	126	134	140	147	155	159	163	167	169
116	121	123	125	127	135	141	148	156	160	164	168	170
117	122	124	126	128	136	142	149	157	161	165	169	171
118	123	125	127	129	137	143	150	158	162	166	170	172
119	124	126	128	130	138	144	151	159	163	167	171	173
120	125	127	129	131	139	145	152	160	164	168	172	174
121	126	128	130	132	140	146	153					

1 20,480, only one culture was observed that could not be agglutinated in a higher dilution than 1 5,120. The results of these tests show that all the para A Pgh cultures are identical with one another.

That all the cultures were not uniformly agglutinated to the titer limit was probably due to the different structures of the agglutination receptors, as the receptors vary in many cases.

The para A Pgh cultures were also agglutinated with para A Schottmueller serum, which had a titer limit of 1 50,000, to prove that the para A Pgh bacillus is identical with para A Schottmueller. The serum used for these tests was obtained from rabbits which had been immunized from cultures isolated from patients Barg and Mueller by Schottmueller.

The serum agglutinated both cultures (Barg and Mueller) in a dilution of 1 50,000 (See Table 6).

The figures in Table 6 show that para A bacillus Pgh and para A Schottmueller are one and the same.

To determine the power of group agglutination, the para A Pgh cultures were agglutinated with para B serum, which possessed a titer limit of 1 50,000 (See Table 7). This serum was obtained from rabbits which had been immunized with a culture from Schottmueller para B, case of Thot.

The greater number of paratyphoid A bacilli are not affected at all by paratyphoid B serum, only three of our cultures were agglutinated by it in a dilution of 1 160. The others were agglutinated in dilutions between 1 20 and 1 80. Group agglutination paratyphoid B serum is very low.

Group agglutination tests were also made with typhoid (Eberth-Gaffky) serum, which had a titer of 1 50,000 for its own bacilli (See Table 8). The results of these tests with para B serum were that Nos 9, 10, 20, 32, 52, 53, 57, 60, 65, 75, 80, 92, 106, 119, 124, 133 and 161 were not affected at all, the highest group agglutination was shown by culture 4, which was slightly agglutinated in a dilution of 1 2,560, an unusually high group agglutination.

The experiments were repeated a number of times to exclude error and gave always the same result. Culture 14 was agglutinated in a dilution of 1 1,200 and 164 in a 1 640 dilution. Group agglutination in 1 320 was shown by Nos 62, 73, 79, 156.

Cultures 13, 16, 33, 113, 145, 163 were agglutinated in a dilution of 1 60. Nos 35, 72, 81, 88, 153 agglutinated in a dilution of 1 80.

Nos 5, 27, 29, 39, 46, 61, 83, 94, 101, 102 agglutinated in a dilution of 1 40, and 1 20 was the highest dilution that would affect Cultures 69, 96 and 97.

TABLE 7—PARA A CULTURES PITTSBURGH, AGGLUTINATED WITH PARA B SERUM SCHOTTMUELLER

Par<sup>n</sup> B, Schottmueller, Case of Thot

Dilution	40960	20480	10240	5120	2560	1280	640	320	160	80	40	20	Culture No																																
40960	0	0	0	0	0	0	0	0	0	0	0	0	+																																
20480	0	0	0	0	0	0	0	0	0	0	0	0	+																																
10240	0	0	0	0	0	0	0	0	0	0	0	0	+																																
5120	0	0	0	0	0	0	0	0	0	0	0	0	+																																
2560	0	0	0	0	0	0	0	0	0	0	0	0	+																																
1280	0	0	0	0	0	0	0	0	0	0	0	0	+																																
640	0	0	0	0	0	0	0	0	0	0	0	0	+																																
320	0	0	0	0	0	0	0	0	0	0	0	0	++																																
160	0	+	0	0	0	0	0	0	+	0	0	0	++																																
80	0	+	0	0	+	0	0	0	0	+	0	0	++																																
40	0	+	0	0	+	0	+	0	0	+	0	0	++																																
20	0	+	0	0	+	0	+	0	0	+	0	0	++																																
Culture No	4	9	10	13	14	16	20	27	32	33	35	39	46	52	53	57	60	61	62	63	69	72	73	75	79	81	83	88	92	94	96	97	101	102	106	113	119	124	133	145	153	156	161	163	164

TABLE 8—PARA A CULTURES PITTSBURGH, AGGLUTINATED WITH TYPHOID SERUM (BACILLUS EBERTH-GAFFKY)

Culture No	(Titel 1 50,000 )									
	Dilution	20	40	80	160	320	640	1280	2560	5120
4	+	+	+	+	+	+	+	+	+	0
5	+	+	0	0	0	0	0	0	0	0
9	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0
13	+	+	+	+	0	0	0	0	0	0
14	+	+	+	+	+	+	+	+	0	0
16	+	+	+	+	0	0	0	0	0	0
20	0	0	0	0	0	0	0	0	0	0
27	+	+	0	0	0	0	0	0	0	0
29	+	+	0	0	0	0	0	0	0	0
32	0	0	0	0	0	0	0	0	0	0
33	++	++	++	+	0	0	0	0	0	0
35	++	+	+	0	0	0	0	0	0	0
39	++	++	0	0	0	0	0	0	0	0
46	+	+	0	0	0	0	0	0	0	0
52	0	0	0	0	0	0	0	0	0	0
53	0	0	0	0	0	0	0	0	0	0
57	0	0	0	0	0	0	0	0	0	0
60	0	0	0	0	0	0	0	0	0	0
61	+	+	0	0	0	0	0	0	0	0
62	++	++	++	+	+	0	0	0	0	0
65	0	0	0	0	0	0	0	0	0	0
69	+	0	0	0	0	0	0	0	0	0
72	++	++	++	0	0	0	0	0	0	0
73	++	++	++	+	+	0	0	0	0	0
75	0	0	0	0	0	0	0	0	0	0
79	+	+	+	+	+	0	0	0	0	0
80	0	0	0	0	0	0	0	0	0	0
81	+	+	+	0	0	0	0	0	0	0
83	+	+	0	0	0	0	0	0	0	0
88	+	+	+	0	0	0	0	0	0	0
92	0	0	0	0	0	0	0	0	0	0
94	+	+	0	0	0	0	0	0	0	0
96	+	0	0	0	0	0	0	0	0	0
97	+	0	0	0	0	0	0	0	0	0
101	++	+	0	0	0	0	0	0	0	0
102	+	+	0	0	0	0	0	0	0	0
106	0	0	0	0	0	0	0	0	0	0
113	++	++	++	++	0	0	0	0	0	0
119	0	0	0	0	0	0	0	0	0	0
124	0	0	0	0	0	0	0	0	0	0
133	0	0	0	0	0	0	0	0	0	0
145	+	+	+	+	0	0	0	0	0	0
153	++	++	+	0	0	0	0	0	0	0
156	++	++	++	+	+	0	0	0	0	0
161	0	0	0	0	0	0	0	0	0	0
163	++	++	+	?	0	0	0	0	0	0
164	++	++	++	+	+	?	0	0	0	0

AGGLUTINATION TESTS WITH CULTURES FROM PREVIOUSLY REPORTED  
CASES†

Serum from rabbits which had been inoculated with paratyphoid A Pittsburgh bacilli and possessed the power of agglutinating the Pittsburgh bacilli in a dilution of 1 40,960, agglutinated cultures from one of Schottmueller's cases (that of Barg), Brion and Kayser's, one of Johnston's cases (that of Milefsky), one of Allen's cases (Samuel), Longcope and Longcope 2026 in the same dilution. The paratyphoid A cultures obtained from Longcope and Longcope 2026 were taken from two of his cases which have not been reported. This serum in a dilution of 1 20,480 agglutinated bacilli from one of Schottmueller's cases (that of Mueller), Coleman and Buxton's, Cushing's O, Hewlett's, Gwyn's (that of Euster), one of Allen's cases and one of Johnston's cases (that of Badach).

Group agglutinations with the following cultures of paratyphoid B was caused by the Pittsburgh A serum Achard and Bensaude's culture W, 1 320, Widal and Nobecourt, 1 160, Rosenau, 1 320, one of Schottmueller's cases (Thot), 1 320, Longcope B, 1 80, Philadelphia B, 1 80, Flexner B was not affected. The *Bacillus enteritidis* (Gartner) 1 160, bacillus of hog cholera, bacillus Hume and bacillus Strong were not affected.

A paratyphoid A serum with a titer limit of 1 40,960 was prepared, using bacilli from one of Schottmueller's cases (that of Barg), both of Schottmueller's cases (Barg and Mueller), Longcope and Longcope 2026 were agglutinated to the titer limit, 1 40,960, cultures from Allen's cases (Euster and Samuels), Cushing O, Brion and Kayser's case, Johnston's cases (Badach and Milefsky), Hewlett's Case 7 and Gwyn's case were all agglutinated in a dilution of 1 20,480, culture from Coleman and Buxton's case was agglutinated in a dilution of 1 10,240.

This serum caused group agglutination of paratyphoid B cultures, Achard and Bensaude's cultures B 1 320, and W, 1 320, Widal and Nobecourt 1 40, Rosenau B 1 40, Philadelphia B 1 40 (?), Longcope 1 160, Schottmueller's case (Thot) 1 320, and Flexner 1 640. *Bacillus* hog cholera, bacillus Hume and bacillus Strong showed negative results, *Bacillus enteritidis* (Gartner) was agglutinated in a dilution of 1 320.

Paratyphoid B Schottmueller serum, with a titer of 1 40,960, had the following group agglutination effect on para A culture Schottmueller's cases (those of Barg and Mueller), Brion and Kayser's case, Coleman and Buxton's, Cushing O, one of Johnston's cases (that of

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† See Tables 9, 10, 11, 12

TABLE 9.—OUTSIDE CULTURES PARA A AND B AGGLUTINATED WITH PARA A SERUM, PITTSBURGH

TABLE 10.—OUTSIDE CULTURES PARA A AGGLUTINATED WITH PARA A SERUM (SCHOTTMUELLER)

TABLE 11.—OUTSIDE CULTURES PARA A AND B AGGLUTINATED WITH SERUM PARA B (SCHOTTMUELLER

TABLE 12.—OUTSIDE CULTURES PARA A AND B AGGLUTINATED WITH TYPHOID SERUM (BACILLUS EBERTH GAFFKY

Milefsky), Allen's cases (those of Euster and Samuels), Hewlett's Case 7, Longcope 2026, Longcope and Gwyn all showed negative results

The paratyphoid B cultures were strongly agglutinated by the same serum as used for the tests with A cultures, one of Schottmueller's cases (that of Thot) in a dilution of 1 40,960, Rosenau 40,960, Achard and Bensaude's B 1 20,480, Flexner B 1 20,480, Longcope B 1 5,120, Philadelphia B 1 5,120, Achard and Bensaude's W 1 10,240, and Widal and Nobecourt 1 10,240, bacillus hog cholera, 1 2,560, *Bacillus enteritidis* (Gartner), 1 320, bacillus Hume and bacillus Strong, negative

Typhoid (Eberth-Gaffky) serum with 1 50,000 titer limit was titrated against all the paratyphoid A and B bacilli obtained from other laboratories. As will appear, none of these group agglutinations were high enough to cause any doubt as to the identity of the organisms. Cushing O gave negative results, one of Johnston's cases (that of Milefsky) was agglutinated in a dilution of 1 20, Johnston's other case (that of Badach), in 1 160, one of Schottmueller's cases (that of Barg), in 1 140, Schottmueller's other case (that of Mueller), in 1 180, Longcope 2026, in 1 160, Hewlett's Case 7 in 1 160, Brion and Kayser's in 1 320, Coleman and Buxton's, in 1 320, one of Allen's cases (that of Euster), in 1 640, and Allen's other case (that of Samuel), was negative. All the above cases were para A.

Paratyphoid B cultures were agglutinated, Achard and Bensaude's W, in 1 640, Achard and Bensaude's B in 1 320, one of Schottmueller's cases (that of Thot), in 1 160, Widal and Nobecourt's, in 1 80 (?), Longcope B, in 1 40, Rosenau B, in 1 40, Flexner was negative and Philadelphia B negative.

#### BACTERIOLYTIC EXPERIMENTS IN VIVO AND IN VITRO

Pfeiffer's<sup>75</sup> test is based on the fact that animals, immunized with cholera bacilli or bacilli of the typhoid coli group, will dissolve the same bacillus as that with which the immunity was produced, when it is injected into the animal's abdominal cavity.

Later Pfeiffer and Metchnikoff<sup>76</sup> showed that this bacteriolytic phenomenon can be observed in a test-tube, by using fresh serum or abdominal fluid. Other investigators then tried to work out a simplified method of performing the test based on the findings of Pfeiffer and

75 Pfeiffer R Die Differentialdiagnose der Vibronen der Cholera asiatica mit Hulfe der Immunisirung Ztschr f Hyg u Infectionskrankh, 1895, p 75

76 Metchnikoff, E Etudes sur l'immunité, sixième mémoire sur la destruction extracellulaire des bactéries dans l'organisme Ann de l'Inst Pasteur 1895, ix 433

## PARATYPHOID A AND PARATYPHOID B

TABLE 13—ONE HUNDRED AND FORTY-EIGHT BACTERIOLYTIC TESTS MADE WITH THE 65 CULTURES OF PARATYPHOID A BACILLI PITTSBURGH, AND PARATYPHOID A PITTSBURGH SERUM

Bacilli Dilution	Inactivated Serum of Rabbit, Immunized with Para A, Pittsburgh	Normal Rabbit Serum as Complement	Number of Colonies on Plates After 24 Hours
	c c	c c	
	0 4	0 3	∞
	0 1	0 3	∞
	0 08	0 3	∞
	0 06	0 3	about 1000
1 c c of a 1 5000	0 04	0 3	about 100
Dilution of a 24 hour old Bouillon Culture	0 02	0 3	about 100
	0 01	0 3	about 50
	0 008	0 3	0
	0 006	0 3	0
	0 004	0 3	100
	0 002	0 3	many 100
	0 001	0 3	many 1000

TABLE 14—THIRTY SIX BACTERIOLYTIC TESTS MADE WITH THE 12 CULTURES OF GWYN, HEWLETT, SCHOTTMUELLER, CUSHING, JOHNSTON, BRION, ROLLY, ALLEN, KAYSER, PLUS PARATYPHOID A, PGH SERUM

Bacilli	Inactivated Serum of Rabbit, Immunized with Para A, Pittsburgh	Normal Rabbit Serum as Complement	Number of Colonies on Plates After 24 Hours
	c c	c c	
	0 4	0 3	∞
	0 1	0 3	∞
	0 08	0 3	∞
	0 06	0 3	about 1000
1 c c of a 1 5000	0 04	0 3	about 100
Dilution of a 24 hour old Bouillon Culture	0 02	0 3	about 50
	0 01	0 3	0
	0 008	0 3	0
	0 006	0 3	0
	0 004	0 3	0
	0 002	0 3	100
	0 001	0 3	1000

TABLE 15—ONE HUNDRED AND EIGHTY BACTERIOLYTIC TESTS MADE WITH THE CULTURES NAMED IN TABLES 13 AND 14, PLUS PARATYPHOID B SERUM

Bacilli	Inactivated Serum of Rabbit, Immunized with Para A, Pittsburgh	Normal Rabbit Serum as Complement	Number of Colonies on Plates After 24 Hours
	c c	c c	
	0 4	0 3	∞
	0 1	0 3	∞
	0 08	0 3	∞
	0 06	0 3	∞
1 c c of a 1 5000	0 04	0 3	∞
Dilution of a 24 hour old Bouillon Culture	0 02	0 3	∞
	0 01	0 3	∞
	0 008	0 3	∞
	0 006	0 3	∞
	0 004	0 3	∞
	0 002	0 3	∞
	0 001	0 3	∞
CONTROLS			
Bacilli 1 5000	0	0	∞
Bacilli 1 5000	0 5	0 5	∞
Bacilli 1 5000	0	0	0
0	1	0	0
0	0	1	0

Metchnikoff Neisser and Wechsberg<sup>77</sup> described a practical method by which a fairly accurate quantitative estimation can be made. Into tubes containing different quantities of serum are put the same amount of culture and fresh complement serum, the tubes are then incubated at 37 C for two hours, at the end of that time a portion of the contents of each tube is agar-plated and a direct count made of the living germs.

At the present time it is the consensus of opinion that while the bacteriolytic test *in vivo* is more difficult to perform than the bacteriolytic test *in vitro*, the former is more accurate and reliable than the latter.

Both bacteriolytic tests *in vivo* and *in vitro* have been extensively used for the identification of the different members of the typhoid-colon group. Stern and Korte<sup>78</sup> and others have found the sera of typhoid and paratyphoid patients possess bacteriolytic properties. The investigations of Stern and Korte show that the bacteriolytic tests are more accurate and constant and finer than the agglutination tests for the identification of the different members of the typhoid-colon group.

Toepfer and Jaffe<sup>79</sup> proved the correctness of Stein's and Korte's communications, and found that nearly all the serums of human beings and animals which had been infected with typhoid bacilli show a bacteriolytic effect on typhoid bacilli *in vitro*. The strongest bacteriolytic effect was produced by serums from people suffering with typhoid fever, the serums of convalescents and artificially immunized persons possessed the power in a lesser degree. After recovery from typhoid fever the serum rapidly loses its bacteriolytic power. The bacteriolytic properties of typhoid patients' serums are specific for the Eberth-Gaffky bacillus and have no effect on paratyphoid A, paratyphoid B colon, or any other bacilli. The serums of three patients who showed unmistakable clinical signs of typhoid fever did not possess bacteriolytic power. Korte states that the blood of typhoid fever patients possesses bacteriolytic power in the first week of the disease. Korte and Sternberg<sup>80</sup> found that the serums from the bodies of those who died of the disease still possessed bacteriolytic power after death.

Toepfer and Jaffe could never find the bacteriolytic properties as strong as Sternberg and Korte could. They could never find sterile

77 Neisser, M., und Wechsberg, F. Ueber die Wirkungsart baktericider Sera. Munchen med Wochenschr, 1901 No 18

78 Stern, R., and Korte, W. Ueber den Nachweis der bakteriziden Reaction im Blutserum der Typhus-Kranken. Berl klin Wochenschr, 1904, No 9, p 213

79 Toepfer und Jaffe. Untersuchungen über die Beziehungen von Baktericidie *in vitro* und im Thierversuch an Typhus und Paratyphusbacillen mit verschiedenen spezifischen Serumproben. Ztschr f Hyg u Infectionskrankh 1906 p 383

80 Korte W., and Sternberg. Weitere Untersuchungen über die Bakterizide des Blutserums der Typhus Kranken. Deutscher Arch f klin Med, 1905, p 321

plates, even when they experimented with the highest concentrated serums, making the agar plates after incubating the serums and bacteria at 37 C for three hours, but when the incubation was continued for twenty-four hours the serum in a dilution of 1 100 showed sterile plates. For the complete action of the bacteriolytic power more than three hours' time is required. Toepfer and Jaffe, also Laubenheimer,<sup>81</sup> could not find as Hahn did, bacteriolytic properties in the serums of people who never had typhoid fever.

Toepfer and Kolle could not find the bacteriolytic action of paratyphoid B serum on paratyphoid B bacilli *in vitro*, but they did observe it *in vivo*. Neisser has shown that the bacteriolytic test *in vitro* may be negative, when by the same serum, *in vivo*, it is strongly positive.

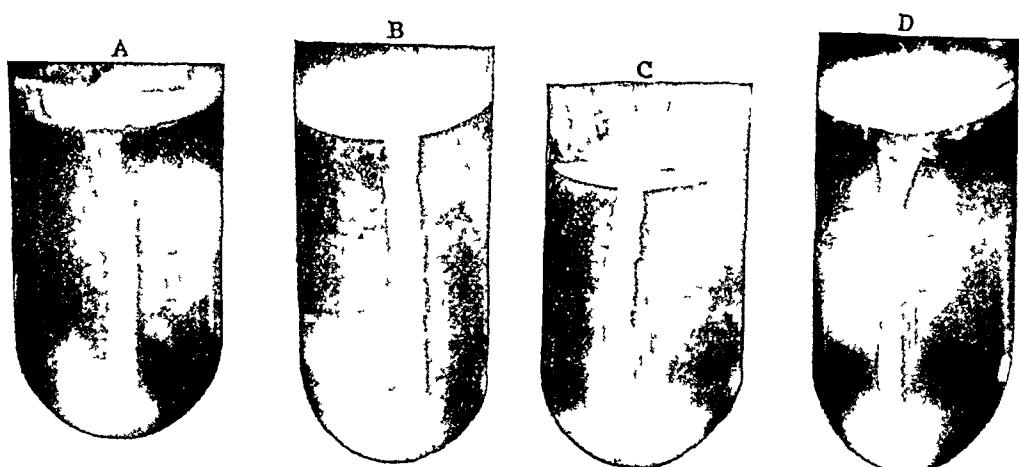


Fig 1.—Stab cultures in gelatin, twelve days old, showing no difference. A, paratyphoid A bacilli, B, paratyphoid B bacilli, C, typhoid bacilli, D, *Bacillus coli communis*.

If the negative results of bacteriolytic tests *in vitro* can be used to show a biological difference between Eberth-Gaffky and paratyphoid B bacilli, as stated by Toepfer and Jaffe, is very questionable.

Laubenheimer found the serum of paratyphoid B patients *in vitro* strongly bacteriolytic, in one case he found, in a dilution of 1 51 200, all the bacilli dissolved. It is probable that there is a difference between bacteriolytic action *in vitro* and *in vivo*. The bacteriolytic action of the serum is the same in both, but perhaps in the living body the tissue cells also play a part in bacterial dissolution.

<sup>81</sup> Laubenheimer, K. Ueber die diagnostische Bedeutung der baktericiden Eigenschaften des Blutserums Typhuskranker. Ztschr f klin Med., Berl., 1905, p 170.

The Pfeiffer experiment *in vivo* when properly performed is less liable to error, gives results in much higher dilutions, and is more exact for the titration of the bacteriolytic power than the test-tube experiment.

The bacteriolytic experiments give specific results, and therefore are more accurate than agglutination tests for the identification of bacteriolytic qualities, but for many reasons the bacteriolytic test is secondary.

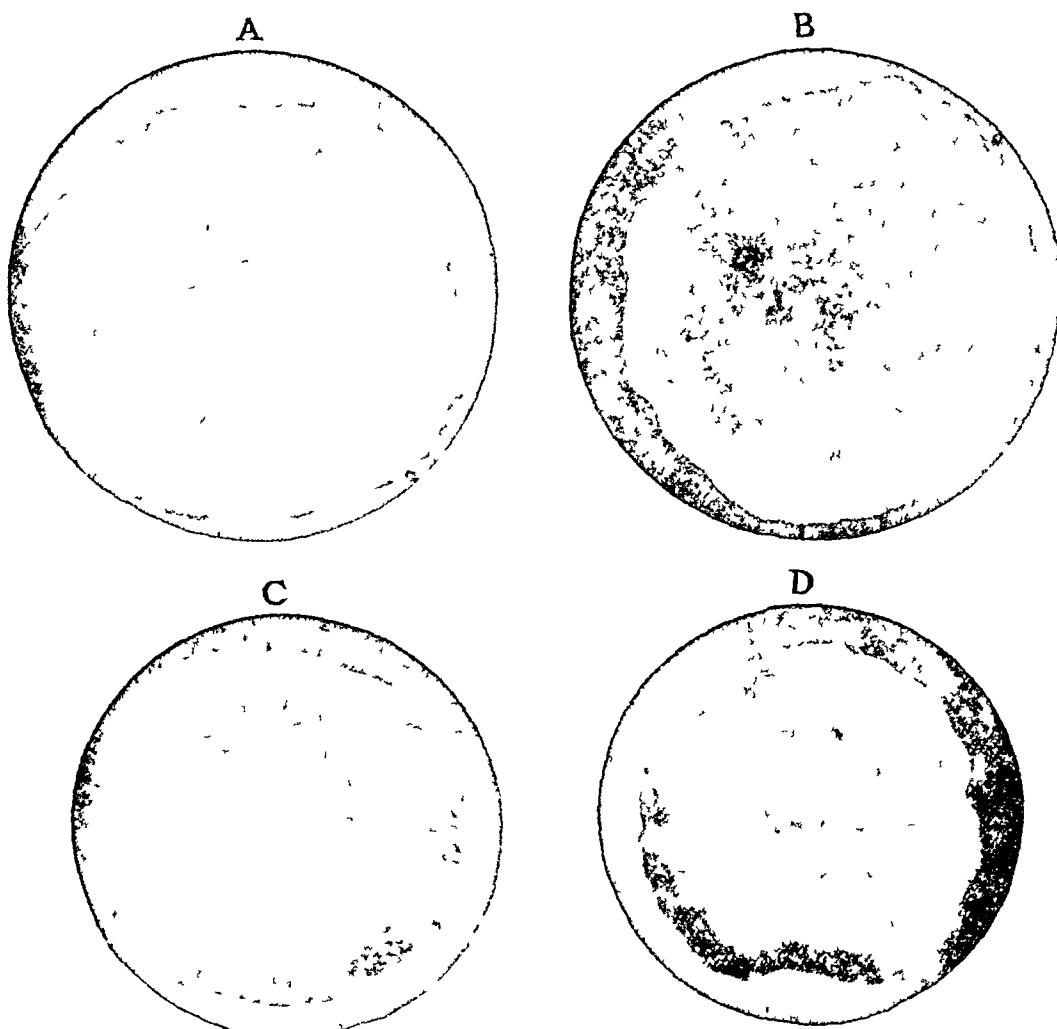


Fig. 2.—Drigalski agar plates, twenty-four hours old, showing no marked difference. A, paratyphoid A bacilli, B, paratyphoid B bacilli, C, typhoid bacilli, D *Bacilli coli communis*.

in importance to the agglutination test as a means of identifying the different members of the typhoid-col<sub>i</sub> group.

Bacteriolytic experiments are more difficult to perform, are much more expensive require more time, labor and apparatus.

Further, individual differences in animals make necessary the repetition of the test four or five times, very much depends on choosing a good

culture, cultures difficult to effect lead to false conclusions so the agglutination test with strongly immunized animal serum is the diagnostic test of election

#### BACTERIOLYTIC EXPERIMENTS

For our bacteriolytic experiments we use the method of Neisser and Wechsberg. The serums used are taken from rabbits which have been injected with dead, and later with living bacilli, such serums possess the property of bacteriolysis in a high degreee. When the immunization of these rabbits is completed, some blood is taken from their ears and the bacteriolytic power is tested, if the test shows that the serum is strongly bacteriolytic, then under strict aseptic precautions the animals are bled from the carotid arteries into glasses. This serum will keep if sterile, without the addition of anything, or may be preserved by the addition of 5 per cent phenol, which has no influence on its bacteriolytic power.

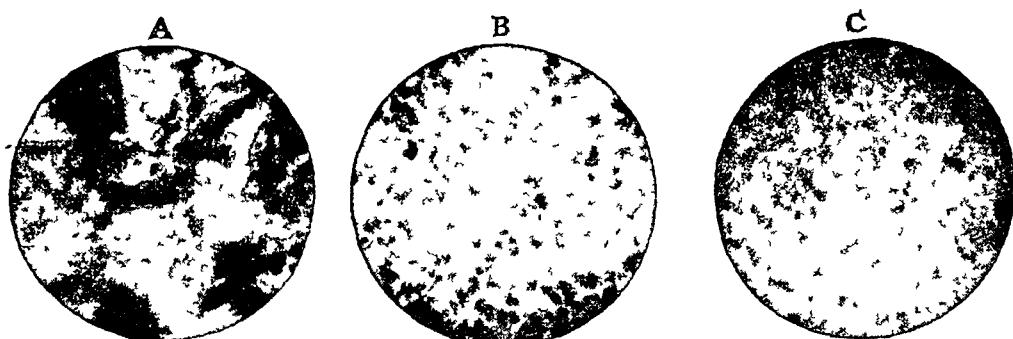


Fig 3.—Agglutination phenomenon, oculai 4, objective 1 (Leitz). A, strongest agglutination, B, midway between A and C, C, agglutination at titer limit

When the fresh serum is used it must be heated to 56 C for half an hour to destroy the complement, because the quantity of complement is unknown, and the presence of too little or too much complement will disturb the experiment. Serum that has been preserved for a long time with 5 per cent phenol need not be heated before using, as the complement has been destroyed by the phenol. The destruction of the complement by heat or preservative leaves an immunifacient, thermostable, bacteriolytic amboceptor, which must be reactivated. The complementation is obtained by adding the serum of a normal animal, the same kind of animal as the immunized serum was obtained from. This serum should be drawn off the clot after the animal's blood has been allowed to stand in a refrigerator for twenty-four hours. The normal serum used as a complement

must show only slight bacteriolytic power, after estimation of the complement-amount the tests are made

A number of sterile test-tubes of 10 cc capacity are placed in a row, we put into them inactivated immune serum as follows 0.5 cc, 0.4 cc, 0.3 cc, 0.2 cc, etc., to the limit of the bacteriolytic power, an equal amount of complement, for example, 0.3 cc, is added. Now 1 cc of bouillon containing the bacteria<sup>82</sup> is put in each tube, finally, a quantity of plain bouillon, sufficient to bring the bulk up to 0.3 cc, is added to each tube, the tubes are shaken to thoroughly mix their contents, after which they are incubated at 37°C for three hours, which is sufficient for the optimum action of the bacteriolytic bodies.

When the tubes are taken from the incubator, 0.3 cc of the contents of each tube is removed with a pipette and mixed with fluid agar at 50°C, the agar is plated, and when the plates have solidified they are turned upside down, and in this position placed in an incubator at 37°C. Pipettes of equal caliber are used in removing the fluid from the different tubes. The agar plates are put in the incubator upside down so that the water of condensation will not fall on the surface of the agar.

The plates are allowed to remain in the incubator for twenty-four hours, at the end of that time they are removed and the colonies counted, for this purpose Wolfhuegel's counting apparatus may be used, microscopic inspection is sufficient to make the estimation. We estimate the number of colonies according to Neisser's method "No growth," "about a hundred" colonies, "some hundreds," "about a thousand," "some thousands," "many thousands," and "uncountable." Great variations in the number of colonies counted on the plates designate differences in bacteriolytic power. The control plates made from tubes which contained no immune serum should show equal amounts of growth and present an uncountable number of colonies.

If the serum is strongly bacteriolytic, sterile plates containing very few germs will be found. Control plates, made from tubes containing only immune serum and complement, should be sterile.

In performing these experiments special attention must be given to complement deviation (Neisser and Wechsberg), because large quantities of immune bodies deviate the complement from the bacilli, through an excessive amount of amoceptor, we recognize this phenomenon by the

<sup>82</sup> An eighteen to twenty-four-hour-old bouillon culture is diluted to 1:5000 by addition of sterile bouillon, and 1 cc of this contains a number of bacteria sufficient to form several thousand colonies on an agar plate, after two to three hours' incubation at 37°C. The agar used in making such plates must be uniform and proved not to cause differences in the growth of the bacteria on any of the plates.

appearance of plates made from tubes containing highly diluted serum and others containing only slightly diluted serum, the appearance of both is the same, all the plates showing luxuriant growth. The plates between these two extremes, of high and low dilution, are sterile.

To avoid errors in performing this test the following controls should be observed:

1 Prove the sterility of serum and complement to be used.

2 Estimate the number of organisms in bacilli dilution.

3 Observe the result of mixing equal amounts of bacilli dilution and complement without immune serum, to make sure the complement possesses no bacteriolytic effect.

4 Mix equal quantities of immune serum and bacilli dilution without complement to learn if inactivated immune serum has not bacteriolytic effect.

5 Prove the sterility of the complement.

In performing bacteriolytic tests much time and labor can be saved by omitting to make agar plates and counting the colonies on them. When the tubes are removed from the incubator they will appear clear or cloudy, if clear they are sterile, cloudiness is evidence of bacterial growth, the results of this quick method are as good as the estimation of colonies on agar plates, in most cases, but very resistant germs, when present, are not killed, but their growth is arrested, tubes containing such organisms will appear clear when removed from the incubator, if agar-plated, they will show bacterial growth, therefore, this abridged method is unreliable and should not be used.

All the paratyphoid A Pgh cultures were entirely destroyed in from 0.006 to 0.008 cc. of the polyvalent paratyphoid A Pgh serum, the amount of this serum required for the complete dissolving of the various other paratyphoid A cultures was not quite the same, some being killed by slightly smaller amounts and others requiring a little more than the quantity necessary for the complete destruction of the Pgh cultures. Paratyphoid-B serum had no bacteriolytic effect on any of the paratyphoid A cultures.

The results of these bacteriolytic tests prove the identity of all the different cultures we have classed as paratyphoid A bacilli.

Each of the forty-eight cultures of paratyphoid A, Pittsburgh, and the cultures of Gwyn, Cushing, Coleman and Buxton, Hewlett, Johnston, Allen, Schottmueller, Brion and Kayser were subjected to the bacteriolytic test, three times, with paratyphoid A, Pittsburgh serum, and three times with paratyphoid B serum.

# THE QUANTITATIVE ESTIMATION OF ALBUMIN IN THE URINE

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The Esbach method is undoubtedly the most widely used simple procedure for the quantitative estimation of albumin in the urine, and, notwithstanding its well-known inaccuracies, it is still used in the majority of laboratories and hospitals. For exact work several accurate quantitative methods are available, but for the clinician the Esbach albuminometer is practically the only quantitative instrument suited to his needs.

A great deal has been written about the Esbach method and its various shortcomings. Emerson and Baumgarten<sup>1</sup> give a series of comparative results obtained by estimation with the Purdy centrifuge and Esbach methods controlled by weighing. They conclude that neither method is satisfactory, and that the Esbach tubes as ordinarily used cannot be relied on for even approximate results. They also state that unless the tubes be kept at a constant temperature, the method is practically useless for comparative quantitative estimations, Christensen's<sup>2</sup> work having shown that differences in temperature of as much as 5° C may cause errors of 100 per cent in the readings.

The chief disadvantages in connection with Esbach determinations as made with the original picric-citric acid solution, may be briefly stated as follows:

1 As ordinarily used the method cannot be depended on for a quantitative estimation of albumin in the urine.

2 Christensen's work has shown that the room temperature should be kept at or near 15° C. Ordinarily this is impossible.

3 Urines must be diluted so that the albumin will read 4 gm per liter or less, if results even approaching accuracy are to be obtained.

4 Urines must be diluted to a specific gravity of 1.006-08 before testing and must be kept at a constant acidity. The specific gravity of the Esbach solution is about 1.012.

\* From the Clinical Laboratory of the Johns Hopkins University and Hospital Baltimore and the Laboratory of Physiological Chemistry Mount Sinai Hospital New York City.

<sup>1</sup> Emerson and Baumgarten Johns Hopkins Hosp Bull, 1903 viii 9

<sup>2</sup> Christensen Virchow's Arch f Path Anat 1889 cxv 128

5 The precipitate does not settle evenly, and it is common to find variations of as much as 1 gm per liter or more between two tubes from the same urine.

6 Even with proper dilution and regard to temperature, urines are occasionally seen, in which the precipitate refuses to settle, or a portion settles, while the rest floats at the top of the tube, readings being impossible.

7 The solution mixes at once with the urine, and the resulting precipitate interferes with a correct reading of the meniscus at the R mark on the tube.

8 The Esbach solution is very disagreeable to handle the picric acid staining clothes and hands in case of accident.

In view of these well-known facts it is not strange that investigators have been searching for a more accurate and simple method for the quantitative estimation of albumin in the urine.

Phosphotungstic acid has long been known as a precipitant for proteins. It is a crystalline organic acid, dissolving readily in water or alcohol, and giving a clear or slightly opalescent solution, which will keep indefinitely if stored in a dark bottle. Boggs<sup>3</sup> found it an ideal precipitant for the proteins in milk, the precipitate appearing immediately in a finely divided condition and settling evenly to a minimum volume in twenty-four hours. The supernatant fluid was perfectly clear and gave no test for protein. Boggs' formula is as follows:

Mix 25 gm phosphotungstic acid thoroughly with 125 cc of distilled water, then dilute 25 cc concentrated hydrochloric acid with 100 cc of distilled water and add to the first mixture.

This solution was used in ordinary Esbach tubes in the same manner as for urine work. Dr W A Baetjer has also used this solution in his work on the proteins in blood, which will soon be published, and has obtained extremely uniform and satisfactory results. Both Boggs and Baetjer controlled their work by quantitative estimations with the Kjeldahl method, and Boggs in over 300 determinations found a mean difference from the Kjeldahl of only 0.2 per cent.

In February, 1908, a paper was published by Tsuchiya,<sup>4</sup> in which he gave the results of a most thorough study of the phosphotungstic method as applied to urine. He found that a watery solution of phosphotungstic acid similar to the one devised by Boggs could not be used with urine, as the phosphates were instantly precipitated and confused the readings. He has found, however, that in the presence of alcohol the phosphates are

<sup>3</sup> Boggs Johns Hopkins Hosp Bull, 1906, xviii, 342

<sup>4</sup> Tsuchiya Zentralbl f inn Med, 1908, xxv, 105

not precipitated or appear only momentarily, disappearing when the urine and acid are thoroughly mixed. His formula is as follows:

Phosphotungstic acid	15 gms
Hydrochloric acid (Conc t.)	5 cc
Ethyl alcohol q.s ad	100 cc

Substituting this in the Esbach tubes for the old picric-citric acid solution, with technic similar otherwise he carried on a long series of experiments, comparing the results with those obtained by the old Esbach method and using a gravimetric control in all cases. The following is a summary of his results:

1. With normal urine there is no precipitate, as sometimes happens with the Esbach reagent.

2. The precipitate from albuminous urines settles more regularly than with the Esbach solution, and foaming or floating of the precipitate is never seen.

3. The method is more exact at ordinary room temperature than is the Esbach.

4. Small amounts of albumin are precipitated as well as large amounts, and this makes the reagent especially applicable to febrile urines.

More recently Goodman and Stein<sup>5</sup> have devised a titration method for the quantitative estimation of albumin in urine, employing Tsuchiya's solution as the precipitant. Five cc of Tsuchiya's reagent are placed in a test-tube and then from a graduated pipette urine is added drop by drop, until the first trace of cloudiness appears. By previous estimations with solutions containing known quantities of egg albumin they determined that 0.1 mg of albumin is the minimal amount which will cause a turbidity in 5 cc of Tsuchiya's reagent. The amount of urine added is read off on the pipette and if 0.1 cc of urine had been used it would be known that 0.1 cc of urine contained 0.1 mg of albumin, and 1,000 cc or a liter would contain 1,000 mg or 1 gm of albumin. They give comparative results of albumin estimation by the Esbach method, Tsuchiya's reagent and their new titration method based on Tsuchiya's reagent. The results were controlled by Engländer's<sup>6</sup> modification of the heat and acetic acid gravimetric estimation. Goodman and Stein conclude that the Esbach method is absolutely unreliable, that Tsuchiya's reagent is an improvement and approaches more nearly the results obtained by weighing while their titration method is startlingly exact varying in but few instances from the gravimetric estimations, and then but slightly.

<sup>5</sup> Goodman E. H. and Stein S. A New Method for the Quantitative Estimation of Albumin in Urine. *Jour Am Med Assn* 1908 li 2055

<sup>6</sup> Engländer. *Zentralbl f Inn Med* 1908 xxix 265

The work which forms the basis for the present article was undertaken in the fall of 1908 at the suggestion of Dr R S Morris and has been carried on both at this hospital and in the laboratory of Dr S Bookman, physiological chemist for the Mount Sinai Hospital, New York City.

The Goodman and Stern titration method was first tested, using prepared solutions of serum albumin in water and normal urine, and also pathological albuminous urines from the wards. Englander's gravimetric method has been used as a control in each case, and in our hands the results given in Table 1 have been obtained.

TABLE 1—TEST OF THE GOODMAN-STERN TITRATION METHOD

No	Diagnosis	Sp Gr	Gravimetric Gm Per Liter	Phos- photungstic Gm Per Liter	Esbach Gm Per Liter	Titration Gm Per Liter
1	Nephritis	1015	2.63	2.45	1.7	10.0
2	Nephritis	1019	2.74	2.6	1.7	10.0
3	Nephritis	1012	3.75	3.5	2.1	12.5
4	Surgical	1014	1.3	1.2	1.0	6.6
5	Nephritis	1018	12.24	11.4	8.1	50.0
6	Nephritis	1017	6.45	6.2	4.3	25.0
7	Nephritis	1016	4.34	4.2	3.4	11.7
8	Nephritis	1014	3.26	3.1	2.0	10.0
9		1022	5.6	5.3	4.1	10.0
10	Cardiac	1017	3.3	3.15	1.8	10.0

The figures in Table 1 have been calculated from readings taken when the first definite trace of cloudiness appeared. According to Goodman and Stein, if a urine contains 1 gm per liter of albumin a cloud should first appear when 0.1 cc of urine has been added to the reagent. If this be true, the albumin content of any urine may be calculated by the following formula:

$$\frac{1 \text{ gm} \times \text{dilution}}{(\text{Number cc of urine added}) - 0.1} = \text{albumin content in gm per liter}$$

For example, urine was added to the reagent from a burette, and the cloud appeared when 0.05 cc had been used. The urine was now diluted ten times, and the titration repeated. The first trace of cloudiness appeared when 0.1 cc of urine had been added. Substituting in the formula:

$$\frac{10 \times 1 \text{ gm}}{0.1 - 0.1} = \frac{10 \text{ gm}}{1}$$

The urine was again diluted ten times, a total dilution of 100. On titration the first trace of cloudiness appeared when 0.7 cc of urine had been added to the reagent. Substituting, again, we have

$$\begin{array}{r} 1 \text{ gm } \times 100 = 100 \text{ gm or } 14.2 \text{ gm per liter} \\ \hline 0.7 - 0.1 \quad 7 \end{array}$$

It is seen that the dilutions do not check. In the 100 dilution cloudiness should not have appeared until 1 cc of the urine had been added. We should then have had the following.

$$\begin{array}{r} 1 \text{ gm } \times 100 \text{ or } 100 \text{ gm } = 10 \text{ gm per liter} \\ \hline 1 - 0.1 \quad 10 \end{array}$$

Table 2 gives more fully the results obtained by diluting the urines.

TABLE 2—RESULTS OBTAINED BY DILUTING THE URINES

No.	Dilution	Gravimetric Gm Per Liter	First Trace of Cloud cc Used	Albumin Gm Per Liter
1	10	2.63	0.1	10.0
	100		0.7	14.2
2	10	2.74	0.1	10.0
	100		0.8	12.5
5	100	12.24	0.2	50.0
	500		0.8	62.5
6	100	6.45	0.4	25.0
	500		1.7	29.4
9	10	5.6	0.1	10.0
	100		0.6	16.6

The crux, then, of the Goodman-Stein method is the determination of the first trace of turbidity. From the results obtained it is evident that, with satisfactory illumination this turbidity has been produced at least in the present experiments, with quantities of albumin less than the minimum determined by Goodman and Stein for egg albumin. Furthermore if the method is a quantitative one, an albuminous urine when diluted, say ten times, should produce the first trace of turbidity with exactly ten times the minimal quantity required with the undiluted urine. But such a result has not been obtained. It has always required relatively less diluted urine (see Table 2) to attain the first turbidity.<sup>7</sup> It is evident therefore, that the albumin or other material which causes the turbidity is not precipitated by Tsuchiya's reagent at a fixed point of concentration. Since the estimated quantities of albumin were invariably very high (see Table 1) when compared with the gravimetric and Tsuchiya's findings the method was discarded, and attention was directed to Tsuchiya's modification of the Esbach method.

<sup>7</sup> To avoid error in noting the first trace of turbidity the tubes were, in most instances inspected independently by numerous other workers in the laboratory. The titrated tubes were placed in a rack with untitrated tubes for controls. In no case did the various observers fail to detect the turbidity in the titrated tubes.

A large amount of preliminary work was done before commencing a systematic examination of pathological urines. Serum albumin was dissolved in distilled water and in normal urine, solutions being thus prepared containing quantities of albumin varying from 0.5 to 7 gm per liter. Duplicate sets of tubes were then treated with the Esbach and phosphotungstic reagents, and after twenty-four hours the results were compared with gravimetric findings. The precipitate from Tsuchiya's reagent invariably settled more evenly and read closer to the weighings than did the Esbach. After further comparisons as to dilutions, specific gravity, acidity, etc., a study of pathological albuminous urines was begun and has been carried on for several months along the following lines:

1 A record has been kept of the diagnosis of the case, together with the specific gravity and reaction of each urine tested.

2 The albumin content of each urine has been estimated by both the Esbach and phosphotungstic methods and controlled in all cases by gravimetric determinations; in all but ten cases the Kjeldahl method has been used as an additional check.

3 In urines with a high albumin content several dilutions have usually been made, each dilution being a check on the one preceding and affording an index to the evenness of precipitation.

4 Studies have been made as to the effects of temperature on precipitation, duplicate sets of tubes being placed in temperatures of 0° C and 37° C and at room temperature.

5 The precipitates obtained with the gravimetric, Esbach and phosphotungstic methods have been tested by Kjeldahl determinations as to relative nitrogen content.

6 A series of normal urines has been tested by both the Esbach and Tsuchiya reagents to determine whether a precipitate occurs under these conditions.

7 A special series has been run to determine what effect, if any, sugar in the urine has on the precipitation of albumin.

8 Experiments have been made to determine whether twenty-four-hour readings are more correct than readings taken at other times.

9 Finally, urines from two patients in the wards of this hospital have been estimated daily for a week to determine whether Tsuchiya's reagent can be depended on to indicate a rise or fall in albumin content.

In neither the phosphotungstic nor the Esbach methods have the urines been diluted to a specific gravity of 1.006-08, the object being to get results which would be given by the method as generally used. All readings given were made at the end of twenty-four hours. For the sake of brevity, readings taken at other hours are omitted.

TABLE 3—TEST OF PHOSPHOTUNGSTIC METHOD AT ORDINARY ROOM TEMPERATURE

No	Diagnosis	Dilutions	Sp Gr	Kjeldahl Gm Per Liter	Gravi- metric Gm Per Liter	Phospho- tungstic Gm Per Liter	Esbach Gm Per Liter
1	Chi nephritis	0	1012	8	8.2	7.5	5.8
2	Chr nephritis	0	1014	4.95	5.15	4.8	3.5
3	Cardiac	0	1018	2.7	2.7	2.6	1.8
4	Nephritis	0	1015	2.48	2.52	2.1	1.6
5	Nephritis	0	1018	3.69	3.71	3.4	2.3
6	Nephritis	0	1022	4.31	4.49	4.2	3.5
7	Nephritis	0	1018	8	8.1	8.8	5.5
		1 to 2		4.0	4.05	3.8	2.5
		1 to 3		2.66	2.7	2.5	1.7
		1 to 4		2	2.025	1.8	1.2
		1 to 5		1.6	1.62	1.5	1.1
		1 to 6		1.33	1.35	1.3	0.9
		1 to 7		1.14	1.157	1.1	0.8
		1 to 8		1	1.01	1.0	0.6
8	Chr nephritis, acute exacerb	0	1020	23.8	24.2		
		1 to 4		5.95	6.05	5.9	2.8
		1 to 8		2.975	3.025	2.9	1.5
9	Myocarditis	0	1016	2.5	2.5	2.4	0.8
10	Chi nephritis	0	1019	14.35	14.05		
		1 to 16		89	878	0.8	*
		1 to 14		1.09	1.003	1+	*
		1 to 10		1.435	1.405	1.3	*
		1 to 8		1.79	1.75	1.75	*
		1 to 6		2.37	2.34	2.3	†
		1 to 5		2.87	2.81	3.0	*
		1 to 4		3.58	3.51	3.7	*
		1 to 3		4.76	4.68	5.0	*
11	Myocarditis	0	1011	1.4	1.41	1.4	†
12	Gen Paresis	0	1015	2.57	2.59	2.7	†
		1 to 2		1.28	1.29	1.2	†
		1 to 3		85	86	0.9	~
13	Nephritis	0	1013	2.43	2.47	2.3	1.0
14	Chr nephritis	0	1018	1.8	1.8	1.7	1.0
15	Pleural effusion	0			46.7		
		1 to 20			2.23	2.6	1.2
		1 to 10			4.67	4.9	3.3

\* Ppt floated, Not settled

No	Diagnosis	Dilutions	Sp Gr	Kjeldahl Gm Per Liter	Gravimetric Gm Per Liter	Phosphotungstic Gm Per Liter	Esbach Gm Per Liter
16	Cardiac	0	1014		3.5	3.5	2.1
17	Nephritis	0	1015		2.63	2.45	1.7
18	Nephritis	0	1019		2.74	2.6	1.7
19	Chr nephritis	0	1012		3.75	3.5	2.1
20	Surgical	0	1014		1.3	1.2	1.0
21	Cardiac	0	1011		3.27	3.1	1.7
22	Nephritis	0	1017		6.45	6.2	4.3
23	Pleural effusion				26.7		
		1 to 5			5.34	5.3	4.3
		1 to 10			2.67	2.3	2.0
		1 to 15			1.78	1.8	0.9
24	Nephritis		1016		4.34	4.2	3.4
25	Nephritis		1016		3.9	3.6	2.1

An inspection of Table 3 clearly shows that at ordinary room temperature the phosphotungstic method is more accurate than the Esbach for both small and large amounts of albumin. In two of the 23 urines the precipitate failed to settle with the Esbach reagent, and in one it floated, such results rarely have been observed with Tsuchiya's reagent. Disturbance of the precipitate is sometimes seen in urines containing an excess of carbonates. It is due to liberation of gas upon addition of the acid reagent, and is easily remedied by first treating the urine with a little acetic acid. The average, greatest, and smallest difference of both methods from the albumin content as given by Kjeldahl and gravimetric determination, is as follows:

	Average Diff	Greatest Diff	Smallest Diff
Esbach	= 1.736	2.8	0.3
Phosphotungstic	= 0.297	0.8	0

In the phosphotungstic method urines need not be diluted to a constant specific gravity, nor need the albumin content be read below 4 gm per liter, as is necessary in the Esbach method. The reagent is itself lighter than water and acts as a diluent for urines with which it is mixed.

The results from two pleural effusions indicate that the method can be used quantitatively in these cases. Tsuchiya has obtained similar results.

All twenty-four-hour readings are approximately correct. Some urines could be read at twelve hours, but this finding is not constant and the saving of time would not be of much practical importance, the twenty-four-hour interval being a very convenient one.

The figures given above are the result of work carried on at all seasons of the year, and it is evident, therefore, that the phosphotungstic method is always reliable, provided extremes of temperature be avoided. The effects of such extremes on both methods are indicated in Table 4. Duplicate sets of tubes were placed in the thermostat and ice-chest, and left at room temperature.

TABLE 4—TEST OF THE PHOSPHOTUNGSTIC METHOD AT VARIOUS TEMPERATURES

No.	Temp.	Diagnosis	Sp Gr	Kjeldahl	Gravi-	Phospho-	Esbach
				Gm Per Liter	metric Gm Per Liter	tungstic Gm Per Liter	
1	Room	Nephritis	1015	3.65	3.68	3.5	1.9
	0°C					7+	U mark
	37°C					1.9	0.8
2	Room	Nephritis	1020	4.76	4.8	4.65	3.2
	0°C					7.5	Above U Mark
	37°C					2.3	Ppt floated
3	Room	Nephritis	1016	3.41	3.42	3.3	2.1
	0°C					6.9	12.0 estimated
	37°C				Contracted	Floated	

The presence of sugar in albuminous urines is of little importance in applying the phosphotungstic method. Tsuchiya's reagent will not precipitate sugar from solution in distilled water or in normal urine.

TABLE 5—PHOSPHOTUNGSTIC METHOD IN SUGAR CONTAINING URINES

Diagnosis	Sp Gr	Kjeldahl Gm Per Liter	Gravimetric Gm Per Liter	Phospho- tungstic Gm Per Liter	Esbach Gm Per Liter
Nephritis	1018	3.9	4	3.8	2.5
+ 2 per cent glucose				3.75	2.4
+ 5 per cent glucose	1030	3.9	4	3.55	2.1

The urine given in Table 5 is one of the several tested, and the results show that a glycosuria of as much as 5 per cent may exist without causing serious error in the phosphotungstic readings.

Tsuchiya states that his reagent does not give a precipitate in normal urine. Fifteen normal urines were tested with his reagent, and a slight precipitate was obtained in each case. Experiment has shown that this precipitate in normal urine does not interfere with readings of 0.5 gm per liter and above. It would be interesting, therefore, to conduct a series of experiments using finely graduated tubes in order to determine just how constant this precipitate in normal urine is, and to what extent it would interfere with albumin estimation in febrile urines. The Esbach

solution gave a precipitate in only 5 of the normal urines, but its precipitation of albumin is too irregular to determine accurately a rise or fall of small amounts. The precipitate thrown down in normal urine by Tsuchiya's reagent is a mixture of organic and inorganic material, consisting largely of phosphates.

Table 6 shows the uniformity with which albumin is precipitated by phosphotungstic acid. Duplicate sets of calibrated tubes have been used with each urine tested, two tubes being filled with the Esbach and two with the phosphotungstic reagent.

TABLE 6—CONTRAST AS TO UNIFORMITY BETWEEN PHOSPHOTUNGSTIC AND ESBACH METHODS

Tube	Diagnosis	Sp Gr	Kjeldahl Gm Per Liter	Gravimetric Gm Per Liter	Phosphotungstic Gm Per Liter	Esbach Gm Per Liter
No 1	Nephritis	1015	2.57	2.63	2.45	1.7
No 2					2.4	1.4
No 1	Cardiac	1011	3.33	3.27	3.1	1.7
No 2					3.1	1.5

These are urines 17 and 21 of the series given in Table 3. Variations of over 0.1 gm are the exception with the phosphotungstic and the rule with the Esbach method, in which variations of 0.5 to 1 gm per liter are not uncommon.

The experiments have been concluded by following daily for a week the urines of two nephritics on the wards of the Johns Hopkins Hospital, to determine whether the Tsuchiya method can be relied on to indicate a rise or fall in albumin content. The results in both cases were entirely satisfactory. The albumin output for a week in Case 1 is shown in the accompanying chart, and an inspection of the chart shows the close parallelism between the Tsuchiya and Kjeldahl methods, as well as the unreliability of the Esbach.

An inspection of all the Kjeldahl and gravimetric estimations shows that the Kjeldahl readings are almost invariably a little under those obtained by weighing. The Kjeldahl estimations were made on the albumin from 10 cc of urine obtained in exactly the same way as for gravimetric determinations, and the two readings should agree exactly. The error must be due to the fact that (a) moisture is not completely expelled from the albumin on drying or is absorbed during weighing, or (b) that the albumin as obtained is not 100 per cent pure according to nitrogen content. The actual nitrogen content of the precipitates thrown down by gravimetric, phosphotungstic and Esbach methods is given in Table 7 according to Kjeldahl estimation made on three different urines.

TABLE 7.—NITROGEN CONTENT OF PRECIPITATES THROWN DOWN BY GRAVIMETRIC, PHOSPHOTUNGSTIC AND ESBACH METHODS

No	— Gravimetric Ppt —		— Phosphotungstic Ppt —		— Esbach Ppt —	
	Nitrogen	Albumin Gm Per Liter	Nitrogen	Albumin Gm Per Liter	Nitrogen	Albumin Gm Per Liter
1	365	2.25	538	3.36	612	3.82
2	64	4.00	7	4.37	824	5.15
3	618	3.86	663	4.137	784	4.9

It is thus seen that both Esbach and Tsuchiya reagents throw down a precipitate which contains more nitrogen than that present in the

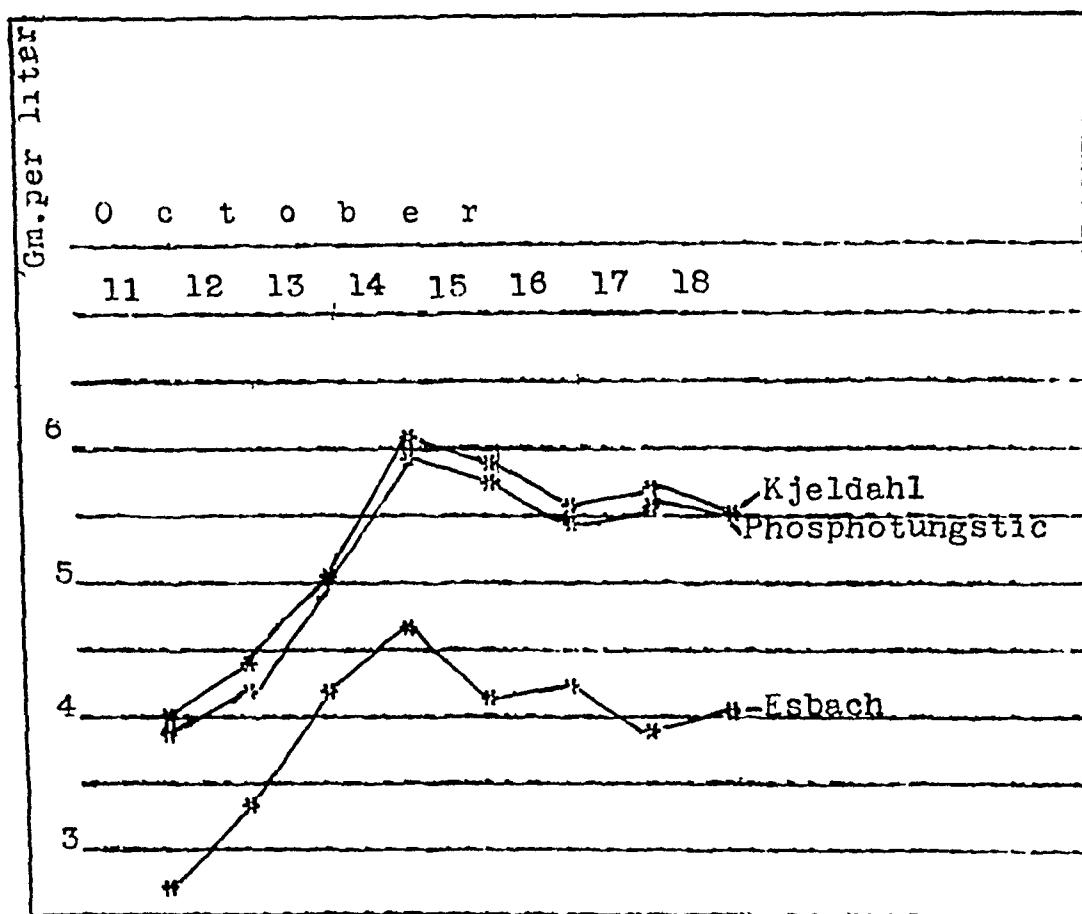


Chart showing albumin output in Case 1 for a week estimated by Kjeldahl, phosphotungstic and Esbach methods.

albumin. Some of the other nitrogenous material in the urine, therefore must be carried down by both precipitates somewhat more so by the Esbach as the results show.

In order to avoid as far as possible the error of personal equation, other workers in the laboratory have been asked to take the readings and many of the figures given above have been so obtained. With slight

exception the results fully confirm Tsuchiya's findings and warrant the following general summary

1 The phosphotungstic method is very much more accurate than the Esbach for a comparative quantitative estimation of albumin in the urine Tsuchiya's reagent should, therefore, supplant the Esbach solution

2 The method can be relied on to indicate a slight rise or fall in albumin output, which is not true of the Esbach

3 Readings are not influenced by changes in temperature to the same extent as with the Esbach

4 Foaming or floating of the precipitate is rarely seen, and the precipitate settles much more evenly than with the Esbach reagent

5 The solution is lighter than water, and when added to urine does not mix until shaken, but rises as a clear supernatant fluid, enabling one to read the meniscus accurately at the R mark on the Esbach tube Because of its low specific gravity the urine needs no further dilution

6 The method can be used for large amounts of albumin as well as for small amounts (See Urine 22, Table 3)

7 Tsuchiya's reagent is applicable in urines where albuminuria and glycosuria coexist

8 Phosphotungstic acid in alcoholic solution is easily prepared keeps well, and does not stain hands or clothes, as does the Esbach reagent

9 Normal urines treated with Tsuchiya's reagent yield a slight precipitate

10 The method of Goodman and Stern has proved to be very inaccurate

In conclusion I wish to thank Dr L F Barker and Dr W S Thayer, also Dr E Libman, for their kindness in placing at my disposal material from their wards, Dr S Bookman for his many valuable suggestions and the use of his laboratory and equipment, and especially Dr R S Morris, to whom I am indebted for advice and assistance throughout the whole course of the work

## THE SEXUAL FORMS OF THE MALARIAL PLASMODIA OCCURRING IN THE BLOOD OF MAN

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The forms of the malarial plasmodia concerned in sporogony which can be differentiated in the blood of the human host are of great interest from both a practical and theoretical standpoint. The presence of these sexual forms, which are intended to complete their development within the mosquito, proves beyond question that the patients in whom they occur are infective to these insects, and that they are thus true "carriers" of malarial disease. The demonstration of these forms is, therefore, of importance in malarial epidemiology and prophylaxis, and as but very brief descriptions of the sexual forms are given in most English and American works dealing with the malarial fevers or the protozoa, it has appeared to me that a detailed account of their morphology, together with a discussion of certain points concerning their rôle in epidemiology, might prove of interest and value to those interested in the diagnosis and prophylaxis of the malarial fevers.

As is well known, there occur in the blood of man, besides the forms of malarial plasmodia concerned in the human cycle of development, or schizogony, certain other forms which are intended to develop only within the mosquito. The observations of Schaudinn<sup>1</sup> regarding parthenogenesis of the macrogamete within man have not been confirmed by many observers and I, although I have most carefully examined many cases, have not been able to demonstrate the forms described by Schaudinn as parthenogenetic forms. Therefore, in the absence of more definite proof than we yet possess I believe that it is the part of wisdom to consider the question of parthenogenesis as an open one and that the sexual forms of the malarial plasmodia occurring in the blood of man are capable of development only within the mosquito.

Of the sexual forms the male are known as microgametocytes and the female as macrogametes while both forms are generally referred to as gametes or gametocytes when spoken of collectively. While no true devel-

<sup>1</sup>This report by Dr. Georg Captain Medical Corps U. S. Army is of work done in the Laboratory of the Surgeon General's office and is published with permission of the Surgeon General of the Army.

1. Schaudinn F. Studien über krankheitserregende Protozoen. Arb. d. k. Gesundh. amte 1902 xix 169

opment of these bodies occurs within man, if the blood containing them be removed from the body, the microgametocytes frequently undergo flagellation and produce fine, motile, filamentous forms, known as microgametes. In very rare instances individual microgametes may be observed to penetrate a macrogamete, representing a process of fertilization normally occurring within the middle intestine of the mosquito.

The differentiation of the sexual forms or gametes is not a very difficult matter although the opposite opinion appears to be generally prevalent. The estivo-autumnal gametes, because of their crescentic shape when fully developed, are easily recognized, even by a novice in malarial parasitology, but the intracorporeal stages of the development of the gametes of all of the species of plasmodia are more difficult of recognition, although with a clear knowledge of their morphology and a little practice, all of their stages of development may be differentiated in stained specimens of blood with the exception of the very earliest intracorporeal stage, in which the morphology is still a matter of dispute. The fully developed gametes of *Plasmodium vivax* (the tertian plasmodium) and *Plasmodium malariae* (the quartan plasmodium) are easily differentiated when one is thoroughly acquainted with their morphology.

In discussing the sexual forms of the malarial plasmodia found in man, it is necessary to consider the gametes in general, and the macrogametes, microgametocytes, and microgametes, of each species, in particular.

#### THE RELATIVE PROPORTION OF MALE AND FEMALE GAMETES

But few observations have been made on the relative proportion of microgametocytes and macrogametes which occur in the peripheral blood of man. As these forms may be readily differentiated, it is rather surprising that the observations upon this phase of our subject are so limited, the best being those of Stephens and Christopher<sup>2</sup> and Ruge<sup>3</sup>. Stephens and Christopher studied the subject in estivo-autumnal infections and found the proportion to be 53 microgametocytes (male) to 33 macrogametes (female), while Ruge, in a large number of benign tertian infections found that the relative proportion varied greatly in different individuals in some there being practically equal numbers of male and female gametes, while in others only one microgametocyte was found to 50 macrogametes.

<sup>2</sup> Stephens J W W and Christopher S R. The Agglutination of Sporozoites, Rep. Malaria Com. Roy. Soc. Lond. 1889-1900 Series 3, p 1

<sup>3</sup> Ruge, R. Fragen und Probleme der modernen Malariaforschung, Centralbl. f. Bakteriol. u. Parasitenk. 1902 VIII, 776

I have frequently observed instances of estivo-autumnal infection in which the proportion of microgametocytes to macrogametes was as 50 to 5, and I believe that in this type of infection the male form always out-numbers the female, and that the same is probably true in tertian and quartan infections.

Sehoudinn<sup>1</sup> asserted that after tertian malarial infections had persisted for some time the microgametocytes gradually disappeared from the peripheral blood, until finally only macrogametes were found. In estivo-autumnal infections I have observed just the opposite, the microgametocytes being the last to disappear from the peripheral blood. It is questionable, however, as to how much weight should be placed on the

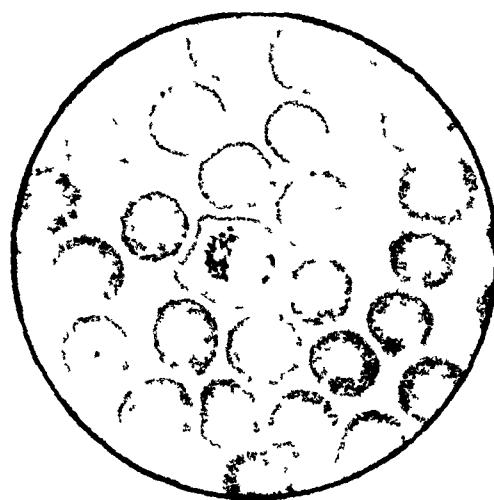


Fig. 1.—A young macrogamete of *Plasmodium vivax* (the tertian plasmodium). Note the darker color and the larger amount of pigment than is present in the microgametocytes shown in Figure 2, the larger size of the organism, and the more distinct outline showing more intense staining.  $\times 1200$

relative proportion of the gametes as observed in the peripheral blood, for it is probable that it is not a true index of the exact proportion present in the body.

#### THE MORPHOLOGY OF THE SEXUAL FORMS OCCURRING IN MAN

In considering the morphology of the sexual forms it is necessary to describe the gametes of each species as observed in both fresh and stained specimens of blood. The description given of the morphology of the various forms will include only the salient diagnostic points and will be found true of the vast majority of the plasmodia examined although frequent deviations will be observed due to pressure in preparing the specimen or artefacts produced during the staining process. The stain which I used was Wright's modification of the Romanowsky method.

## THE SEXUAL FORMS OF PLASMODIUM VIVAX (THE TERTIAN PLASMODIUM)

*Fresh Preparations*—In flesh preparations it is practically impossible to distinguish the gametes of *Plasmodium vivax* from the schizonts (forms of the human cycle) until they are fully developed. While individual gametes may contain a larger amount of pigment, which is coarser in structure, than do the schizonts, this distinction cannot always be made, while the hyaline stage cannot be distinguished by the loss of the "ring-form," as this form is frequently absent in tertian infections in which gametes have not developed. When the gametes are fully developed, however, they may be easily distinguished from the fully developed schizont, and the male and female forms may be readily differentiated.

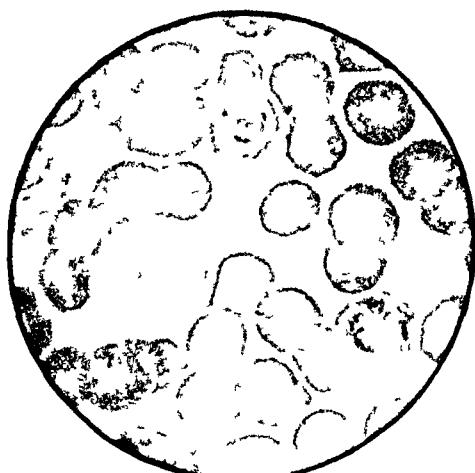


Fig. 2.—Two young microgametocytes of *Plasmodium vivax*. Note the lighter color and smaller amount of the pigment, and the less distinct outline, showing the poor staining quality of this form of the plasmodium.  $\times 1200$

*The Living Macrogamete*—The tertian macrogamete, when fully developed, measures from 9 to 11 microns in diameter, and is perfectly circular in shape, the protoplasm appearing more granular than that of the mature schizont, while the pigment, instead of being distributed throughout the protoplasm, is arranged in the form of very large grains, clumps or rods, about the periphery of the organism, or in a wreath-like manner at some distance from the periphery. The pigment is not motile and the organism appears more refractile than the schizont. Very rarely a flagellum or microgamete may be observed attached to this form of the parasite, but the character of the movements of the flagellum and the peculiar arrangement of the pigment within the macrogamete serve to distinguish it from a flagellating microgametocyte.

*The Living Microgametocyte*—The microgametocyte of *Plasmodium vivax* is slightly smaller than the macrogamete, measuring, when fully

developed, from 8 to 10 microns in diameter, it is spherical in shape, the protoplasm is less granular, and the pigment is generally distributed throughout the protoplasm. The pigment is larger in amount than in the macrogamete and is sluggishly motile when the organism has just been liberated from the red corpuscle in which it has developed. In the fully developed form the pigment may be immotile, and in such instances, instead of being collected in clumps about the periphery of the red cell, or in a wreath-like manner near the center, as in the macrogamete, it is scattered in minute clumps throughout the protoplasm.

The phenomenon which distinguishes the living microgametocyte from all other forms of malaria plasmodia is the process known as flagel-

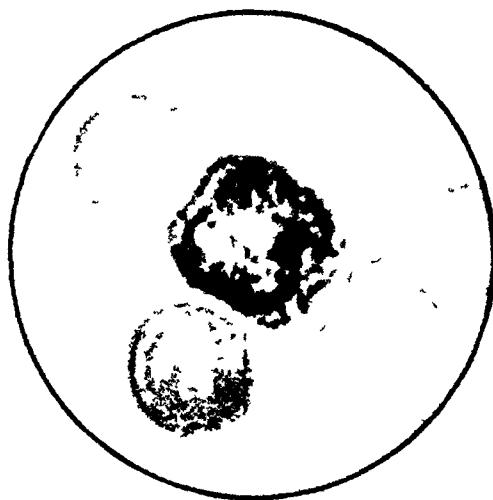


Fig. 3.—A fully developed macrogamete of *Plasmodium vivax*. Note dark, rod like pigment granules, the chromatin collected in a dense mass at one side of the organism, and the distinct appearance of the organism due to the deep staining of the protoplasm.  $\times 1500$

lation during which the microgametes, which have developed within the microgametocyte, are finally extruded and liberated from the parent body. The microgametocytes which are about to undergo this change are easily recognized because of the violent activity of the pigment within them, and the undulatory movements of the border of the parasite. This violent activity of the pigment is due to the flagella of microgametes moving about within the parent body and if such an organism be carefully watched it will be observed that eventually a number of delicate filaments suddenly make their appearance at the periphery of the organism and lash about in the blood plasma. These are the microgametes and vary in number from two to four. They are perfectly hyaline in appearance although not infrequently a few granules of pigment may be observed within them, derived from the microgametocyte. Before the occurrence

of flagellation the pigment of the microgametocyte tends to collect toward the center of the organism and is arranged in a more or less compact mass.

After lashing about for a variable time, one, or perhaps all, of the microgametes succeed in freeing themselves from the parent body, and disappear among the red blood corpuscles. In rare instances one of these free microgametes may be observed attached to a macrogamete, but this is altogether exceptional, and such bodies should be distinguished from a flagellating microgametocyte.

*The Living Microgamete*.—In fresh blood preparations the microgamete appears as a thread-like, hyaline body, which possesses a serpentine motility, enabling it to progress among the red blood corpuscles which are moved about during its passage. It is often discovered in fresh prep-

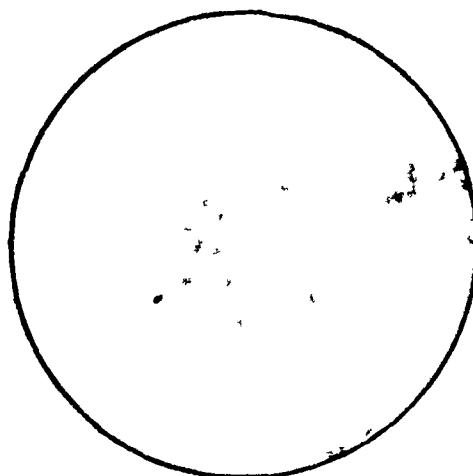


Fig. 4.—A fully developed microgametocyte of *Plasmodium vivax*. Note the fine pigment granules, the larger amount of chromatin, arranged in a loose network, instead of in a solid mass, as in the macrogamete, and the indistinct appearance of the organism due to its poor staining quality.  $\times 1500$

arations by the very apparent movement of the erythrocytes in its vicinity. As a rule, the microgametes are very slender bodies, but sometimes short stout forms are observed, the significance of which has not been determined. Very frequently one extremity of the microgamete is clubbed, while the opposite extremity is sharply pointed, but usually after liberation both extremities are sharply pointed. The length of the microgamete varies the usual measurement being from 16 microns to 20 microns, but forms have been observed measuring as much as 40 to 50 microns, or even more. A few pigment granules may sometimes be observed within the microgametes and this pigment is apparently rapidly extruded, for no pigment is ever observed in microgametes which have

become attached to macrogametes. The variation in the length of the microgametes is more marked in the tertian species than in the quartan or estivo-autumnal species, and short, rather thick forms are frequently observed along with long slender forms in infections with this parasite.

*Stained Preparations*.—Unlike fresh preparations, in stained preparations the young intracorporeal stages of the tertian gametes may be recognized. This is true of all but the very earliest intracorporeal stage, in which the gamete is with great difficulty differentiated from the schizont. While this is true, it is possible, even before the development of pigment to differentiate the gametes by their staining reactions. When stained by the Wright method all forms of the malarial plasmodia present the same fundamental staining reactions but differences are observed in the intensity of the reaction in the various stages of growth and in the

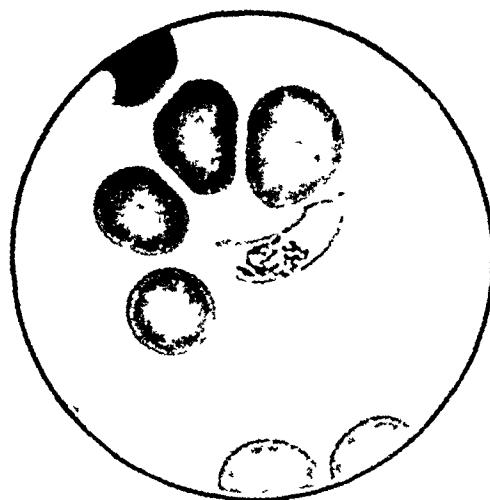


Fig. 5.—A macrogamete of *Plasmodium falciparum* (the tertian estivo-autumnal plasmodium). Note the slender form of the crescent, which is characteristic of the macrogametes.  $\times 1500$

forms concerned in sporogony and schizogony. The protoplasm stains blue; the chromatin of the nucleus a bright red or violet while the achromatic portion of the nucleus remains unstained. The only variation which occurs in the staining reaction of the gametes consists in the degree of color imparted by the stain to the various forms. The tertian gametes when stained by this method consist of a mass of blue protoplasm enclosing the red-stained chromatin; the achromatic portion of the nucleus is not always distinct and the young gamete is considerably larger than the young schizont. The pigmented gamete contains more pigment than do the developing schizonts, while the chromatin shows no evidence of division and distribution throughout the protoplasm being arranged in small irregular masses confined to one portion of the organism or broken up

into fine fibrils surrounded by an unstained area, which is again surrounded by the blue-stained protoplasm. While intracorporeal, the gametes are always spherical in shape, but are sometimes distorted during the preparation of the specimen. The following data are of service in differentiating tertian gametes from tertian schizonts:

1. The young, intracorporeal gamete is never "ring"-like in shape, as the achromatic zone is imperfectly defined.
2. The gamete is larger than the corresponding stage in growth of the schizont.
3. The pigment in the gamete is larger in amount and earlier developed.
4. The chromatin is arranged in a loose skein or in minute masses and is not distributed throughout the protoplasm at any stage in the development of the gamete.

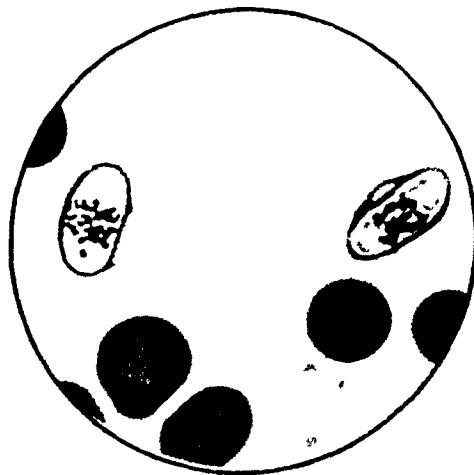


Fig. 6.—Two microgametocytes of *Plasmodium falciparum*. Note the plump kidney shape which is characteristic of the microgametocytes of the estivo-autumnal plasmodia.  $\times 1500$

5. When sporulating parasites are present the gametes are easily recognizable, for, though larger than the sporulating bodies, they present no evidence of segmentation of the chromatin.

*The Stained Macrogamete*—In stained specimens the tertian macrogamete stains a very intense blue and the intensity of the staining serves to distinguish this form of the plasmodium from the schizont or the microgametocyte. The chromatin, in the earliest stage of development consists of a small dot situated near the center of the organism, while in later stages of development several dots or rods of this substance are present, situated near the periphery of the organism, but it is not distributed throughout the protoplasm. The chromatin is comparatively small in

amount and stains a brilliant crimson. The pigment is almost black in color in stained preparations and arranged in irregular masses near the periphery or in a wreath-like manner about the center of the parasite. The pigment is usually in the form of rods, measuring from 1 to 3 microns in length.

*The Stained Microgametocyte*—In stained specimens the microgametocytes of *Plasmodium vivax* vary in appearance during the various stages of development. The young microgametocytes stain a very pale blue and contain a comparatively large dot of intensely stained chromatin. The fully developed microgametocytes present a very poorly stained protoplasm, the blue tinge being so faint in many instances as to be distinguished with difficulty, the protoplasm appearing hyaline. The chromatin is always large in amount in all stages of development and stains an intense red. In microgametes which are about to liberate flagella, the chromatin is observed to be divided into from four to eight masses, which are arranged about the periphery of the organism, and these forms are sometimes mistaken for sporulating quartan plasmodia. The pigment is larger in amount than in the schizonts or the macrogametes, and stains a greenish blue color. It is in the form of fine grains or short very slender rods. If microgametocytes which have liberated the microgametes or flagella be studied in stained specimens before the microgametes have separated from the parent body, it will be observed that the chromatin of the parent body may be traced into the flagella. In some instances it will be seen that all of the chromatin has become collected in the microgametes, the microgametocyte being free from this substance, although in most instances a few irregular clumps, minute in size, may still be observed within it. It is evident from this observation that most of the chromatin of the microgametocyte is expended in the formation of the microgametes.

The chromatin in the microgametocytes is always larger in amount than in the macrogametes, and is collected in the form of rather thick fibrils arranged in irregular masses in the protoplasm, the whole being surrounded by an achromatic zone. It is never distributed in regular masses throughout the protoplasm as it is in the schizonts prior to or during sporulation. In stained specimens the shape of the microgametocyte is oval or circular but it may be distorted during the preparation of the specimen.

*Differentiation of the Tertian Microgametocyte from the Macrogamete*—The microgametocyte of *Plasmodium vivax* may be readily differentiated from the macrogamete by attention to the following points:

1 The microgametocyte is smaller than the macrogamete

2 In fresh specimens the microgametocyte has a greater amount of pigment than the macrogamete and the peculiar "swarming motion" of the pigment serves to differentiate this form of the plasmodium from the full-grown schizont, in which the pigment is motionless, and from the macrogamete, in which the pigment is arranged in a wreath-like form and is either motionless or very sluggishly motile. The pigment in the microgametocyte is in the form of fine granules or very short slender rods, while in the macrogamete the pigment is in the form of large thick rods.

3 The protoplasm in living specimens of the microgametocyte is less granular in structure

4 The presence of the microgametes or flagella in the microgametocyte and the process of flagellation. While flagella may very rarely be seen attached to macrogametes, it is generally easy to distinguish this form because of the peculiar character of the motility of the microgamete in its endeavor to penetrate the macrogamete.

5 In stained specimens the greenish-blue stain of the protoplasm in the microgametocyte serves to distinguish it from the macrogamete, in which the protoplasm is stained a deep blue.

6 The microgametocyte has a larger amount of chromatin, collected in masses, the whole surrounded by an achromatic zone, while in the macrogamete the chromatin is small in amount and is in the form of minute dots or very delicate fibrils, collected near the periphery of the parasite, surrounded by an achromatic zone.

*The Stained Microgametes*—In stained preparations the microgametes or flagella of *Plasmodium vivax* are observed to be composed of a slender lengthened mass of protoplasm which stains a pale blue and which contains a certain amount of chromatin, stained a brilliant crimson. The chromatin may be situated near the center of the organism in the form of a more or less regular mass, or it may be distributed throughout the protoplasm in the form of minute granules, or extend in the form of a broken thread along the greater portion of the length of the microgamete. Before liberation from the microgametocyte the microgametes often present a free clubbed extremity, but after they have become detached from the parent organism the extremities are always pointed. In general appearance the microgametes resemble the spirochetes, but they are not regularly curved and, of course, the staining reactions, and the more delicate appearance of the microgametes serve to distinguish them from the latter. The chromatin is very large in amount in the microgamete and not infrequently organisms are observed in which it is very difficult to distinguish any proto-

plasm, the entire organism appearing to be composed of chromatin. For this reason the microgametes are often overlooked in the examination of malarial blood, but if attention is paid to this point it will be found that not a few stained preparations contain this form of the organism.

### THE SEXUAL FORMS OF PLASMODIUM MALARIAE (THE QUARTAN PLASMODIUM)

*Fresh Preparations*—The gametes of *Plasmodium malariae* are very similar to those of *Plasmodium vivax*, and for this reason will be described but briefly. In their early stages of development they cannot be distinguished from the schizonts, in flesh blood, but when they are fully developed they may be distinguished by their larger size, the absence of sporulation, and the greater amount of pigment present.

*The Living Macrogamete*—The quartan macrogamete is larger than the schizont when fully developed and differs from the latter in possessing a more granular protoplasm and a greater amount of very coarse pigment. We cannot depend on the motility of the pigment and its arrangement in differentiating this form of the quartan plasmodium, for in the quartan schizont the pigment is often observed to be arranged in large clumps about the periphery, but a well-marked wreath-like arrangement of the pigment about midway between the center of the organism and the periphery is very characteristic of the macrogamete. The process of flagellation is never observed in this form of the organism.

*The Living Microgametocyte*—The description of the microgametocyte of *Plasmodium vivax*, already given, applies equally well to the microgametocytes of *Plasmodium malariae*. We observe the same development of microgametes or flagella, the same relative proportion of pigment, and the same peculiar "swarming" motility in this pigment. In size the quartan microgametocyte is slightly larger than the tertian. The pigment is coarser in character than in the tertian microgametocyte.

*The Living Microgamete*—The microgamete of the quartan plasmodium is smaller than that of the tertian, but is otherwise similar. I believe that if it were possible to compare the two forms in flesh specimens, the quartan form would be found to be considerably thicker than the tertian and less actively motile. Aside from the difference in length, which may amount to several microns, it is impossible to distinguish the tertian from the quartan microgamete.

*Stained Preparations*—In stained preparations the gametes of *Plasmodium malariae* resemble very closely those of the tertian plasmodium, though they are smaller and stain more intensely. In their earliest intra-

corpuscular stages of development they may be distinguished from the schizont by the situation of the chromatin dot within the ring of protoplasm and the absence of a distinct achromatic zone. When fully developed they may be distinguished by their larger size, the difference in their staining reactions, the absence of indications of sporulation, and the arrangement and amount of the chromatin.

*The Stained Macrogamete*—The protoplasm of the macrogamete stains a deep blue and the chromatin a dark crimson. When fully developed the macrogamete measures from 10 to 12 microns in diameter, so that it is considerably larger than the fully developed schizont, the chromatin is collected at some portion of the periphery in the form of fine fibrils or small masses, surrounded by an unstained space, the pigment is coarse and is distributed throughout the protoplasm, and there is never any indication of the division of the chromatin, so characteristic of the schizont when it has reached the same size. The shape of the organism is always oval or circular when the smears have been carefully prepared.

*The Stained Microgametocyte*—The protoplasm of the quartan microgametocyte stains a pale blue which serves to distinguish it very readily from the deep blue macrogamete. The chromatin is large in amount, stains a deep red or violet, and is arranged in a loose skein composed of definite fibrils or granules, situated to one side of the center of the organism. It never shows the evidences of division characteristic of the chromatin in sporulating parasites. The quartan microgametocyte is much smaller than is the tertian and the staining reactions are more pronounced.

*The Stained Microgamete*—The microgametes of *Plasmodium malariae* are indistinguishable in stained preparations from those of *Plasmodium vivax*, and the description already given of the latter answers equally well for the microgametes of this species.

#### THE SEXUAL FORMS OF THE ESTIVO-AUTUMNAL PLASMODIA

The sexual forms of *Plasmodium falciparum* (the tertian estivo-autumnal plasmodium) and of *Plasmodium falciparum quotidianum* (the quotidian estivo-autumnal plasmodium) are commonly known as "crescents," and these are the only malarial gametes having a crescentic shape. For this reason, when fully developed they are very easily differentiated from the estivo-autumnal schizonts, and from the tertian and quartan gametes. In the young intracorporeal stage of development the crescentic shape is not present, and at this time the estivo-autumnal gametes are indistinguishable from those of the quartan species. When fully developed the male and female gametes are very easily distinguished.

from one another. It should be remembered that the presence of crescentic gametes invariably indicates an estivo-autumnal infection, and further, that such infection is transmissible to the mosquito.

The differences between the gametes of the tertian and quotidian estivo-autumnal plasmodia consist chiefly in variation in size and shape, the general morphology of both species being identical. For this reason they will be considered together, the salient points of difference being spoken of in the general description.

The estivo-autumnal gametes, like those of *Plasmodium vivax* and *Plasmodium malariae*, develop within the red corpuscles, from which they are finally liberated by the degeneration of the latter. The microgametocytes then undergo flagellation and produce the microgametes, the crescentic microgametocyte having previously become oval and then spherical in shape. The macrogametes also become oval and spherical in shape before fertilization by the microgamete, and it is probable that important maturation changes occur in this form during this period of development.

*Fresh Preparations*.—The earliest stage in the development of the estivo-autumnal gamete cannot be differentiated from the young schizont, but after the formation of pigment the gametes are distinguished by a larger amount of the latter, their ovoid or crescentic shape, even in early stages of development within the red corpuscle, and their slighter degree of ameboid activity. The protoplasm of the gametes, especially of the macrogametes, is more granular in structure, the pigment is darker in color, and the organism is more refractive and sharply outlined. As development proceeds the infected red cell shrinks about the gamete, forming an envelope, which is very noticeable between the poles of the crescent, where it projects and forms what is known as the "bib" of the crescent.

*The Living Macrogamete*.—The macrogamete of *Plasmodium falciparum*, when fully developed, measures from 11 to 15 microns in length, and from 3 to 5 microns in breadth, while that of *Plasmodium falciparum quotidianum* measures from 8 to 9 microns in length. In both species the macrogametes are distinguished from the microgametocytes by their more slender form and the arrangement of the pigment. The protoplasm of the estivo-autumnal macrogametes is very opaque and granular in appearance even in early stages of the development of the organism within the red corpuscle. The pigment is dark brown in character, and after the destruction of the infected red cell is arranged in a dense mass or in a wreath-like manner, at or near the center of the organism. The fully developed macrogamete possesses a clearly cut single outline, a very granular opaque protoplasm, and a considerable amount of rod-like pig-

ment, situated near the center of the crescent. Preparatory to fertilization the crescentic form is lost, the macrogametes first becoming oval in outline, and then circular, while the pigment becomes divided into small clumps arranged in a perfect circle surrounding the center of the parasite. Reasoning from analogy, it is probable that during this change in shape important changes are occurring in the nuclear chromatin, in the nature of reduction phenomena. Such changes have not as yet, however, been demonstrated. While the production of the ovoid and round forms from the macrogamete occurs normally within the middle intestine of the mosquito, the process is very frequently observed in blood which has been removed for some time from the body. The quotidian estivo-autumnal macrogamete is smaller than the tertian form, has a smaller amount of pigment, which is granular rather than rod-like in structure, a less granular protoplasm, while the extremities of the crescent are pointed instead of rounded, as they are in the tertian estivo-autumnal macrogamete.

*The Living Microgametocyte*.—The microgametocyte of *Plasmodium falciparum*, when fully developed, measures from 7 to 10 microns in length, and from 4 to 6 microns in breadth, while that of *Plasmodium falciparum quotidianum* measures from 6 to 7 microns in length and is slightly broader than the tertian microgametocyte. Both are kidney-shaped rather than crescentic, a fact which renders their differentiation from the estivo-autumnal macrogametes a matter of little difficulty. The protoplasm is less opaque and granular than that of the macrogametes, while the pigment is in finer particles and may be distributed throughout the protoplasm of the crescent or even collected in clumps at one pole of the crescent. The pigment is generally sluggishly motile, while the parasites are still intracellular and become very actively so just prior to flagellation.

After the total destruction of the red corpuscle in which they have developed, the estivo-autumnal microgametocytes flagellate in the same manner as do the microgametocytes of the tertian and quartan plasmodia. The kidney shape is lost, the organism becoming ovoid and round, the pigment becomes very motile, the protoplasm appears violently agitated, and suddenly the microgametes are extruded as very delicate, motile filaments, numbering from two to four, and, rarely, even more. After lashing about for a while the microgametes become detached from the parent body and disappear among the red corpuscles. This process occurs naturally in the middle intestine of the mosquito, but may frequently be witnessed in blood containing microgametocytes, after it has been removed for some time.

The quotidian estivo-autumnal microgametocyte differs from that of the tertian estivo-autumnal species in the following particulars: smaller size, seldom measuring over 7 microns in length, the smaller amount of pigment, and the very plump shape of the organism, closely resembling that of a lima-bean.

*The Living Microgametes*—The microgametes of the estivo-autumnal plasmodia are indistinguishable from those of the tertian and quartan plasmodia, consisting of delicate, motile filaments, resembling spirochetes in fresh blood preparations. We possess no data which enable us to differentiate the microgametes of the various species of the malarial plasmodia from one another in either fresh or stained material.

*Stained Preparations*—In stained preparations the estivo-autumnal gametes are easily differentiated from the schizonts, even in an early stage of development. Before the development of pigment the gametes may be distinguished from the schizonts by their spherical shape and the lack of the "ring" form so characteristic of the estivo-autumnal schizont. At this stage of development the gamete consists of a circular portion of protoplasm, which stains blue, enclosing a dot or minute clump of chromatin, stained a deep red or violet. After the development of pigment the gametes are distinguished by their ovoid or crescentic shape, even while contained in the red corpuscle, the presence of a larger amount of chromatin, and the presence, in properly stained specimens, of a deep red band encircling the parasite. When fully developed the gametes are most easily distinguished by their crescentic shape.

*The Stained Macrogamete*—The staining reactions of the estivo-autumnal macrogametes are the same as those of the tertian and quartan forms, i.e., the protoplasm stains a deep blue and the chromatin a brilliant red or violet. The protoplasm stains most intensely in the young intracellular macrogametes and this is also true of the chromatin. When fully developed the protoplasm of the crescentic macrogamete stains deeply blue, the color being most intense at the poles of the crescent, not infrequently deeply stained areas are observed, especially numerous near the poles of the crescent. The chromatin is situated at or near the center of the macrogamete, stains a light red or pink, and is not infrequently obscured by the pigment which being collected at the center of the organism appears to be mixed with the chromatin. In many instances the chromatin is observed to lie at the center of the crescent, surrounded by a perfect ring of pigment granules. Many interesting variations are noted in the staining reactions of the macrogametes, most of them due to pressure during the preparation of the specimen, or to artefacts produced during the staining process.

The remains of the red blood corpuscle surrounding many of the macrogametes stains a salmon or pink color, thus forming a smooth pink border to the crescent, or this border may be broken and jagged in appearance, or missing at some portion of the periphery of the crescent. The so-called "bib" of the crescent is often beautifully shown in stained specimens, consisting of a faintly stained pink mass lying within the concavity of the crescent, the projecting border staining a deeper pink or red. Such gametes are still intracorporeal, although the crescentic shape is fully developed.

Some of the macrogametes, which are apparently extracorporeal, present a very deeply stained red border, the nature of which is still uncertain. A similar red border is not infrequently observed surrounding the young intracorporeal gametes, so that it is not probable that it is due to the substance of the infected red corpuscle. In addition, the staining reaction is different, the protoplasm of the red corpuscle staining a light red or pink, while the edge of the gamete stains a deep red, very similar to the staining reaction observed in the chromatin.

The following features serve to distinguish the estivo-autumnal macrogametes from the microgametocytes in stained preparations:

- 1 The long slender shape of the crescents
- 2 The character of the chromatin which is situated at or near the center of the crescent in a dense mass or irregular clump
- 3 The deep blue staining of the protoplasm
- 4 The concentration of the pigment at or near the center of the organism, in the form of masses, or in wreath-like manner, surrounding the chromatin

*The Stained Microgametocyte*—The protoplasm of the microgametocyte stains a delicate robin's-egg blue, very different from the deep blue or purple of the macrogamete. In some instances the protoplasm refuses to stain. The chromatin is arranged in the form of a loose network composed of delicate fibrils and granules which stain a deep pink or light red. Sometimes the chromatin appears to be divided into several clumps distributed throughout the protoplasm. The pigment is distributed throughout the protoplasm, stains a greenish brown, and is in the form of fine granules or very short rods. Some portions of the microgametocytes stain more intensely than others, giving the crescent a peculiar blotchy appearance, and sometimes only the border of the crescent takes the stain. The chromatin not infrequently stains so poorly as to be barely distinguishable. The remains of the red blood corpuscle, in which the microgametocyte has developed, stains in the same manner as described for the macrogamete. The chromatin of the ovoid and round forms,

which develop from the microgametocyte, is arranged in small clumps about the periphery and stains a deeper red than while the organisms are crescentic in shape.

The points already mentioned in distinguishing the tertian estivo-autumnal microgametocyte from the quotidian are observed in stained specimens of blood, and, in addition, it is found that the quotidian microgametocyte contains a larger amount of more intensely stained chromatin, while the protoplasm also stains a deeper blue than does that of the tertian estivo-autumnal microgametocyte.

The estivo-autumnal microgametocyte may be readily differentiated from the macrogamete by attention to the following points:

- 1 Shape The plump kidney shape
- 2 Staining reaction The pale blue staining of the protoplasm and the less intense staining of the chromatin
- 3 Chromatin The arrangement of the chromatin in the form of a loose network
- 4 Pigment The distribution of the pigment throughout the protoplasm
- 5 Size The microgametocytes are shorter and broader than are the macrogametes

The above description of the morphology of the sexual forms of the malarial plasmodia observed in fresh and stained specimens of human blood includes only those points which are of importance in diagnosis, many minute details of the structure of these interesting bodies have not been touched on for the reason that they can be studied only where a large amount of material is available, are not of importance from a diagnostic standpoint, and are not of constant occurrence. It is believed that attention to the differential details described in this paper should enable any one, with a little practice, to be able to diagnose these forms.

#### PERCENTAGE OF PATIENTS IN WHOM GAMETES OCCUR

As only those individuals in whom the sexual forms, or gametes occur are capable of transmitting malaria to the mosquito and thus, indirectly, to man, it is of interest to know how large a percentage of our malarial patients become "carriers." The number will vary, of course, in different localities owing to conditions favoring the persistence of the infection, the type of infection present, the thoroughness with which treatment is carried out and perhaps other conditions with which we are as yet unfamiliar. This subject has been most thoroughly studied in estivo-autumnal infections because of the ease with which the crescentic gametes are recognized. The data we possess show beyond question that the percentage of

patients having gametes in their peripheral blood varies considerably in different localities and that the incidence of gametes in the peripheral blood cannot be taken as a true index of their actual occurrence in the body, for in many instances it has been demonstrated that blood obtained by splenic puncture will be found full of gametes when none can be found in the peripheral blood. Rogers<sup>4</sup> observed crescents in only 10 per cent of the cases he studied in Europe, while Deaderick<sup>5</sup> states that in his experience they are very rarely observed in the peripheral blood. In my experience gametes have been observed in a little over 33 per cent of my cases of estivo-autumnal infections. A longer search might have considerably increased this percentage, for it often requires the patient examination of several specimens of blood to demonstrate the presence of crescents in estivo-autumnal infections. In the instances of recurrent infection in Filipinos whom I studied, to whom no quinin had been administered for weeks or months, crescents occurred in fully 80 per cent of the infected individuals, and were as numerous in the adult Filipinos as in the children. Manson<sup>6</sup> believes that the estivo-autumnal gametes are more frequently observed in patients who have contracted their malaria in the tropics and have returned to temperate regions, and that gametes are more rarely observed in the tropics. I cannot confirm this opinion, as in my experience as large a proportion of patients in the Philippines, if untreated, show gametes as in the United States. Soldiers returning from Cuba and the Philippines, and suffering from recurrent malaria after their return, did not show a larger percentage of infections with crescents than soldiers serving in those countries and suffering from malaria while there, and it is not at all uncommon to observe crescents in the peripheral blood of the Filipinos.

From what has been said it is evident that the percentage of cases showing estivo-autumnal gametes varies considerably, but it may be said, without danger of contradiction, that a large majority of our patients will develop these bodies unless they are properly treated with quinin. I believe, from my observations on a native race, the Filipinos, that at least 80 per cent of our estivo-autumnal patients will become carriers of this type of infection unless thoroughly treated.

We possess but very little data concerning the percentage of patients infected with the tertian and quartan plasmodia in whom gametes develop

<sup>4</sup> Rogers, L. Malarial Remittent Fevers, *Jour Trop Med and Hyg*, London, 1903, Sept 1, p 272

<sup>5</sup> Deaderick, W H. A Practical Study of Malaria Ed 1 Philadelphia, 1909, W B Saunders & Co

<sup>6</sup> Manson, Sir P. Tropical Diseases, Ed 4, New York, 1907, William Wood & Co

I have found that about 50 per cent of tertian and quartan infections which I observed showed a few gametes in the peripheral blood, provided the infections had persisted for some time and quinin had not been administered during the first week or two of the infection. Here again, it is not safe to infer that no gametes are developed because they may not be demonstrable in the peripheral blood, as it is probable that in these infections as in the estivo-autumnal gametes would be often found in the spleen and bone-marrow.

While the absence of gametes from the peripheral blood would appear to demonstrate that the individual is not a carrier of malarial infection, and while, for practical purposes, such individuals have to be considered as safe in this respect, it does not follow that such is really the case for the gametes may be present in the internal organs and find their way into the peripheral circulation at intervals in sufficient numbers to infect mosquitoes, or they may be present in such small numbers in the peripheral blood as to render their demonstration impossible, and yet the blood may be infective. As regards the latter statement it should not be forgotten that other blood protozoa, such as the trypanosomes and spirochetes, often occur in numbers so small in the peripheral blood as to render their demonstration impossible, although the blood is infective to animals. A great deal of work needs to be done on this subject before we can be sure of our premises, and the recent experiments of Darling<sup>7</sup> are a step in the right direction. His observation that the peripheral blood must contain a certain number of gametes in order to be capable of infecting the mosquito is very suggestive, but needs confirmation by a large number of experiments.

#### THE TIME OF OCCURRENCE OF THE SEXUAL FORMS

It is universally admitted that gametes do not develop until the malarial infection has persisted for several days uninfluenced by quinin. The length of time required for the development of the gametes of the estivo-autumnal plasmodia varies from eight to fifteen days the usual period being about twelve days. In other words an estivo-autumnal infection must have persisted for nearly two weeks before we can expect to find crescents in the peripheral blood. The gametes of *Plasmodium vivax* and *Plasmodium malariae* appear in the peripheral blood in from seven to ten days after the onset of definite symptoms of infection.

It should be remembered that the malarial infection may have been present for a considerable time before the occurrence of definite symptoms.

<sup>7</sup> Darling S. T. Transmission of Malarial Fever in the Canal Zone by Anopheline Mosquitoes. Jour. Am. Med. Assn. 1909, Jan. 2051.

so that the actual time required for the development of gametes may be much longer than is generally supposed from our examinations of the peripheral blood after the occurrence of symptoms. Again, the blood may contain gametes before any symptoms of malarial infection have been noted. I have observed gametes in cases of latent malaria in which no malarial symptoms had ever occurred, so that we may find these sexual forms present on the very first day of an obvious infection.

The fact, however, that several days elapse after the occurrence of symptoms before gametes appear in the peripheral blood, in the vast majority of patients, is of the greatest importance from a prophylactic standpoint, as will be mentioned later. It is also very significant as regards the origin of these bodies, and appears to indicate that they are not introduced into man by the mosquito, but that, as Schaudinn<sup>1</sup> believed, they are differentiated during the human life cycle of the plasmodia as the result of the reaction of the human system to the plasmodia. Certainly all of the evidence we possess points to this conclusion.

#### THE EFFECT OF QUININ ON THE SEXUAL FORM

The consensus of opinion is that after the gametes of the various species of plasmodia are fully developed quinin has no action on them, so far as their development within the mosquito is concerned. In the early intracorporeal stages I have observed marked changes in their staining reactions which lead me to believe that during this period in their development quinin is capable of injuring them and preventing their full development, for the protoplasm and chromatin stains atypically and the latter is reduced in amount. If quinin be given promptly during the initial attack of fever it will effectually prevent the development of gametes in the vast majority of infections, in those cases in which it does not do so it is probable that the infection has been present for some time in a latent state and that gametes have developed before the appearance of symptoms.

The experiments of Schoo,<sup>8</sup> while not confirmed, appear to indicate that the tertian gametes may sometimes be prevented from development in the mosquito by the administration of quinin. He found that in two tertian cases, the patients being bitten by *Anopheles* before the administration of quinin, nearly all of the insects became infected, while the same individuals, bitten after the administration of this drug, were unable to infect any of the insects. These observations are at variance with those

<sup>8</sup> Schoo, F. Wat kan er aan Prophylaxis der Malaria in Nederland gedaan worden? Nederl Tijdschr Geneesk, 1902, xvii, 974

of many investigators and should be carefully repeated. The fact that no morphologic changes occur in the fully developed tertian gametes after the administration of quinin is pretty good evidence that the drug cannot affect them so seriously as to prevent their further development in the mosquito.

No morphological changes occur in the fully developed quartan or estivo-autumnal gametes after the administration of quinin to patients in whom these forms are present. The estivo-autumnal crescents are capable of development within the mosquito even though the drug has been administered for weeks, as has been proven by Marchiafava,<sup>9</sup> Gualdi,<sup>10</sup> Martirano<sup>11</sup> Darling<sup>7</sup> and others. On the Isthmus of Panama Darling<sup>7</sup> found that the development of malarial gametes in the middle intestine of *A. albimanus* was not affected by quinin "when such an infected mosquito feeds daily or on alternate days for fifteen days on patients who are receiving 30 grains of quinin in solution daily. In these instances the zygotes mature and sporozoites reach the salivary glands in the usual period."

The observations of Darling prove that the administration of quinin to patients whose blood contains tertian and estivo-autumnal gametes results in the gradual disappearance of these forms from the peripheral blood. He found that the administration of 30 grains of the drug in solution per day was capable of reducing the number of crescents in the peripheral blood from 67 per 100 leucocytes to 1 per 200 leucocytes in twenty-five days, while in another case the crescents were reduced from 92 per 100 leucocytes to 1 per 100 leucocytes in fifteen days. On the other hand, in cases in which quinin was not administered the crescents appeared to increase rather than diminish in the peripheral blood. As the result of these experiments Darling concludes that the administration of quinin in gamete-carriers is of the greatest importance in the prophylaxis of malarial disease.

#### NUMBER OF GAMETES NECESSARY FOR INFECTION OF THE MOSQUITO

It is but reasonable to believe that the peripheral blood must contain a certain number of gametes in order to render it infective to the mosquito but I know of only one investigator who has undertaken to prove

<sup>9</sup> Marchiafava I. Malaria Twentieth Century Practice xix Ed 1 New York 1900 William Wood & Co

<sup>10</sup> Gualdi I. and Martirano, I. L'azione della chinina sulle semilune. Atti d'ing. speri. 1901 xi 6

<sup>11</sup> Martirano I. Ann d'ing. speri. 1901 xi 6

the number necessary for such infection. In a very ingenious series of experiments Darling<sup>7</sup> has arrived at the conclusion that the peripheral blood must contain at least 12 crescents per cubic centimeter or more than one per 500 leucocytes in order to be infective to the mosquito, and that patients whose blood contains this number should be regarded as gamete-carriers and kept in hospital until, by the administration of quinin, the number is reduced below this minimum. Darling arrived at his results by comparing the number of crescents present with the number of leucocytes, estimating the amount of blood ingested by the mosquito in biting by weighing the insect both before and after eating, and then calculating the number of crescents contained in the amount of blood ingested. While the results of these experiments are very suggestive, it should be remembered that many factors have to be considered in making such comparisons. The presence of a slight or marked leucocytosis, local congestions, factors determining the number of gametes present in the peripheral blood and in the internal organs, all have to be carefully weighed in reaching a true understanding of the significance of such investigations.

As regards the reduction in the number of gametes in the peripheral blood after the administration of quinin, we should not be too hasty in concluding that such reduction means the destruction of these bodies, for it is much more probable that they are simply driven from the peripheral circulation to the spleen and bone-marrow, for we possess no data showing that quinin produces any changes whatever in the morphology of the fully developed gametes. The disappearance of the gametes from the peripheral blood may, of course, render the blood non-infective for the time being but we do not know how long a period elapses before the gametes may reappear in the peripheral circulation and the blood become infective. It appears to me that, while it may be good practice to keep our malarial patients in the hospital until the gametes are reduced to the number mentioned by Darling, it would be better to keep them until the gametes entirely disappear from the peripheral blood. Even then we should not be too sanguine as regards the future non-infectivity of such patients for many malarial patients relapse in whom no gametes can be demonstrated in the peripheral blood.

#### CONCLUSION

From what has been said regarding the action of quinin on the malarial gametes it is evident that if we thoroughly treat our malarial patients during the initial attack of the disease we shall prevent the formation of

these bodies and, therefore, the transmission of the infection to the mosquito. A great deal of the malaria prevalent in every malarial locality is directly traceable to improperly treated patients, and the prophylaxis of the disease will be immensely helped by the thorough treatment of every infection. The practice of regarding such infections as cured because the active symptoms have disappeared is a most common and a most pernicious one, and one that is responsible for the transmission of a very large proportion of malarial disease. Every malarial patient should be kept on quinin for at least a week or two after the disappearance of symptoms, and should take the drug, in 10-grain doses, once a week for two months after the acute attack.

### III THE COMPARATIVE VALUE OF VASOMOTOR DRUGS IN RENAL HEMORRHAGES

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#### I INTRODUCTION

Since the lowering of blood-pressure during hemorrhage contributes materially to its natural diminution, it is argued that a further reduction in pressure should favor a more prompt cessation. This doctrine, so frequently emphasized as fundamental in the treatment of bleeding, loses sight of the important fact that, during a hemorrhage, all the protective mechanisms of the body are called into play to maintain the blood-pressure, so that the brain, which is the organ most susceptible to anemia, shall receive a supply approaching the normal. To accomplish this the peripheral vessels constrict, the heart beats faster and lymph flows in from the surrounding tissues<sup>1</sup>. Consequently, I have contended that any agent that counteracts these mechanisms is as unphysiological as those that increase the bleeding.

A study of the effect of vasomotor drugs on the activity of the respiratory center during hemorrhage has strengthened this view. If an anesthetized animal, but one not under the influence of morphin, is allowed to die from repeated hemorrhages, it is found that, first, a stimulation and later a depression of the respiratory center occurs. The normal regular respirations are gradually supplanted, first by a type in which long inspirations periodically recur, then, as the loss of blood continues, by a type characterized by an increase in rate and depth of inspiration, and often by an active expiration. This is the stage of active stimulation. Following this, respiration again becomes slow and shallow, finally ceasing altogether. A subsequent gasp or two marks the end. Now it follows that a sudden lowering of pressure by vasodilating drugs during any stage of hemorrhage brings on a type of breathing of the next lower order. An animal whose respiration is still normal becomes dyspneic (Fig. 1), in one that already gives evidence of respiratory stimulation, the breathing becomes more shallow and often ceases. In each case the

\* This investigation, one of a series of studies in inaccessible internal hemorrhages, was carried out during the summer of 1909 at the Research Laboratory of Parke, Davis & Co., Detroit, Mich.

<sup>1</sup> Frédéricq Travaux du Laboratoire de Liège 1885

respiratory center is set a notch toward the side of death. If, on the other hand, the pressure is raised, the respiration reverts to a preceding type. An animal in marked dyspnea calms down to quiet breathing (Fig. 2), and one whose respiration has entirely stopped may even be aroused to respiratory activity. In each case the respiratory center is set a notch toward the side of recovery.

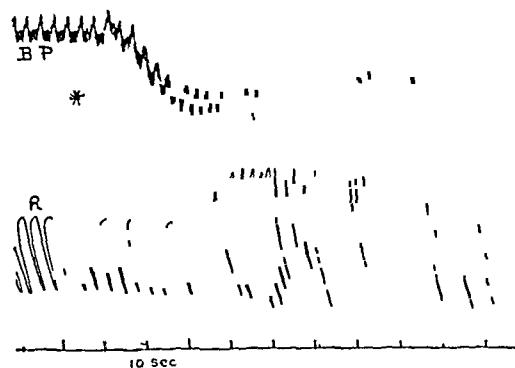


Fig. 1.—Record showing dyspnea induced by lowering the blood-pressure during a hemorrhage by  $1/100$  grain nitroglycerin (administered at point indicated by star), B P, blood-pressure, R, respiration, down stroke, inspiration, up-stroke, expiration.

These observations emphasize the importance of using drugs in internal hemorrhage which, by their introduction into the body, shall not only check the bleeding, but shall also simultaneously elevate the arterial pressure. Having already investigated the hemostatic value of certain

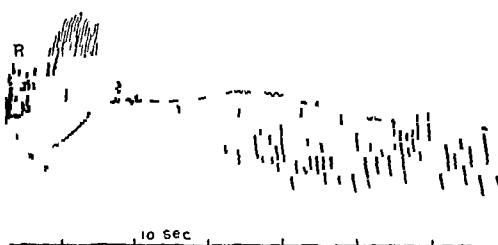


Fig. 2.—Record showing beneficial influence exerted on an existing dyspnea by raising the pressure during hemorrhage by 0.01 mg adrenalin. Lettering same as before.

pressure-raising drugs on hemorrhages derived from intestinal and pulmonary vessels, it became of interest next to investigate their comparative hemostatic value in renal hemorrhages.

## II TYPES OF RENAL HEMORRHAGE AND THEIR EXPERIMENTAL PRODUCTION

Renal hemorrhages may be classified according as they are derived (a) from large arteries, (b) from small vessels and capillaries, or (c) from veins. Fortunately, the vascular arrangement of the kidney is such

that, by appropriate incisions, each type may be created and studied experimentally. The cortex of the kidney contains almost entirely vessels of small caliber, hence a cortical incision wounds only the smaller renal vessels. In the posterior row of renal calices there is an area, according to Brodel,<sup>2</sup> where an incision avoids the large arteries, but wounds the large collecting veins. An incision made about 5 mm posterior to the convex border is followed, as a rule, by a slow stream of dark blood, indicating that a venous hemorrhage has been created. To supplement this study, the flow from one of the renal veins was in a number of cases directly measured. Large arterial hemorrhages were created by deep incisions made on the anterior surface of the kidney. The bright color of the blood, the spouting stream and the rapid fall in pressure left no doubt as to the source of bleeding. Previous to making these incisions, the kidney was brought through a cut in the abdomen and held outside by a partial closure of the wound by hemostats. To record the flow of blood from these kidney wounds, the animal was fixed on an inclined animal board so that the kidney came directly over the pan of the hemorrhage-recording apparatus.

### III ADRENALIN AS A HEMOSTATIC

#### *In Cortical Hemorrhages*

Sixteen experiments to determine the influence of adrenalin on cortical hemorrhages were made. In these it was found without exception that 0.02 to 0.1 mg of adrenalin injected intravenously caused a prompt diminution of hemorrhage synchronous with the rise in pressure. The larger the dose administered the more complete was the checking of the bleeding. As the pressure returned to normal, however, the loss of blood increased again, though never to such an extent as before injection (Fig. 3 c). The permanent decrease is accounted for by the fact that clot formation was favored during the action of adrenalin.

When the intravenous injection of a 1:200,000 solution was continued for from three to four minutes slowly, instead of being injected rapidly, or when 0.5 to 1 mg was given intramuscularly (Fig. 4), the decrease in hemorrhage became permanent and the rise of pressure was prolonged.

#### *In Venous Hemorrhages*

Ten tests showed that adrenalin in doses ranging from 0.01 to 0.1 mg caused, as in cortical hemorrhages, a decrease in bleeding synchronous with the rise in blood-pressure. Larger doses were more effective than the smaller ones. The reduction in the bleeding differed, however,

<sup>2</sup> Brodel Bull Johns Hopkins Hosp., 1901, vii, 10

from that noticed in cortical hemorrhages by remaining permanent after the pressure fell (Figs 3 and 4) The explanation of this difference is apparently simple Adrenalin reduces bleeding from the veins largely through its constriction of the small arterioles, and the diminished flow of blood into the veins facilitates clot formation over the wound As the small arteries relax after the adrenalin action has passed off, the clot which has partially occluded the bleeding veins is not directly interfered with

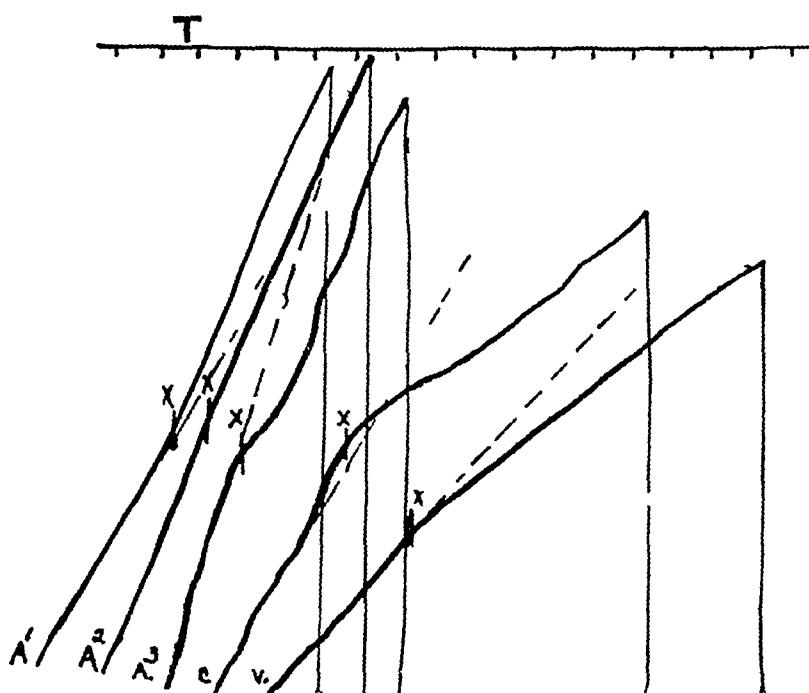


Fig. 3.—Five curves illustrating effect of adrenalin on the various types of renal hemorrhage Transferred from separate records by means of a pantograph A<sup>1</sup>, A<sup>2</sup>, A<sup>3</sup>, effects of 0.05 to 0.002 and 0.005 mg of adrenalin respectively on arterial hemorrhage, c, effect of 0.02 mg adrenalin on cortical hemorrhage, v, effect of 0.02 mg adrenalin on venous hemorrhage, T, time in 10-second periods, x, points where adrenalin action began

#### *In Arterial Hemorrhages*

Twenty-one tests showed that the influence of adrenalin on these hemorrhages was less favorable With the rise of pressure following a single intravenous injection the bleeding sometimes increased, sometimes decreased, and often remained unaltered The results evidently bear a direct relation to the dose injected Thus, as shown in Fig 3, A, 0.05 mg caused an increase in bleeding, 0.01 mg no change and 0.005 mg a decrease Evidently there is, in the larger arteries, an antagonism between its local action on these vessels and the rise of blood-pressure occasioned, and only doses which elevate the pressure but little are

adequate to check bleeding. Intramuscular injections which raise the pressure slightly but permanently distinctly favored cessation.

### Summary

Although most renal hemorrhages are probably derived either from the smaller arteries or the veins, the possibility of their origin from the large arteries of the kidney must not be overlooked. Since it is practically impossible to differentiate between the different forms of hemorrhage it becomes imperative to use such a dose of adrenalin as is not detrimental in any form. Reference to a tabular summary will facilitate the selection of such a dose.

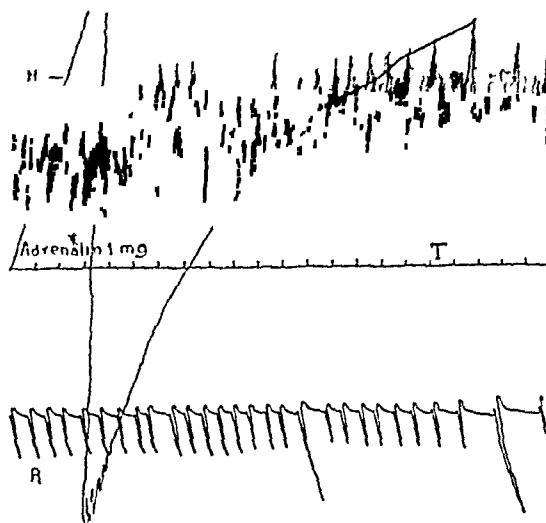


Fig 4.—Effect of 0.1 mg adrenalin given intramuscularly. H, cortical hemorrhage; B, P, blood-pressure; T, time in seconds; R, respiration.

### SUMMARY OF THE EFFECT OF VARIOUS DOSES OF ADRENALIN

Dose	Cortical Hemorrhage	Venous Hemorrhage	Arterial Hemorrhage
Intravenous dose 0.01-0.02 mg	Fair decrease lasting during rise of pressure	Fair decrease permanent	Slight decrease or no change
Intravenous dose 0.05-0.1 mg	Marked decrease lasting during rise of pressure	Marked decrease or cessation, permanent	Slight or marked increase while pressure remains up
Slow and prolonged intravenous injection 0.01-0.04 mg per minute	Decrease, later cessation	Marked decrease or cessation	Slight decrease, cessation favored
Intramuscular dose 0.5 to 1 mg	Prompt cessation, permanent	Prompt cessation, permanent	Slight decrease, or no change

From a consideration of the above summary we may draw the following conclusions:

1 Large doses of adrenalin (0.05 to 0.1 mg), which are peculiarly powerful in checking venous and cortical renal hemorrhages, actually augment the bleeding from the large arteries

2. Smaller doses (0.01 to 0.02 mg), causing a fair decrease in cortical and venous hemorrhages, also cause a decrease of arterial hemorrhages, or at least do not increase them. These are the doses of choice when a differential diagnosis is impossible

3 The slow intravenous introduction of a 1:200,000 solution of adrenalin favors checking of all hemorrhages at the same time that the rise of pressure is permanent.

#### IV THE INFLUENCE OF PITUITARY EXTRACT

The use of pituitary extract as a pressure-raising drug possesses the advantage over adrenalin that it causes a prolonged rise of pressure after a single intravenous injection, which makes it especially valuable to maintain a proper supply to the brain during hemorrhage. Accordingly, an investigation of its value as a hemostatic in renal hemorrhages seemed desirable. For this purpose the pituitary extract prepared by Parke, Davis & Co., according to the method described by Aldrich<sup>3</sup>, was tested intravenously in doses of 0.5 to 2 cc.

#### Results

The results of thirty-six injections showed that pituitary extract exerted a far less favorable influence on renal hemorrhages than did adrenalin. In the venous and cortical types of hemorrhage it was frequently found that an elevation of arterial pressure of from 10 to 20 mm was accompanied by a gradual decrease in bleeding, though many times no change occurred (Fig 5). The diminution never occurred with the promptness or completeness characteristic of adrenalin. This observation suggested the query whether the decrease in bleeding was due to the action of pituitrin or appeared merely as a coincidence in these cases. Three sets of experiments inclined me to the latter view. First, pituitary extract never caused a decrease in arterial hemorrhages, in fact, it distinctly increased them when the pressure rise exceeded 10 to 15 mm. Second, the flow of blood from a renal vein tended, when the blood had been rendered non-coagulable, rather to increase than decrease after its administration (Fig 6). Third, oncometer tracings of the kidney taken in ten experiments showed that the kidney volume also followed the blood

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<sup>3</sup> Aldrich Am Jour Physiol, Proceedings of the Society, 1908, xx1, 23

pressure (Fig. 6). The changes were never opposite or showed even temporary signs of such a tendency as was the case with adrenalin. These observations are in accord with the results of Magnus and Schafer,<sup>4</sup> who also found that, though the volume of the spleen, intestines and limbs diminished that of the kidney always increased after pituitary extract.

These results show conclusively that any decrease in bleeding which occurred could not have been due to the influence of the extract on the renal vessels, but must be attributed rather to the natural coagulation process.

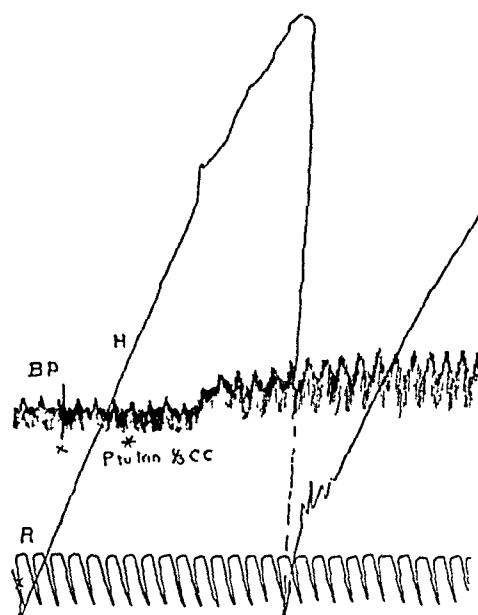


Fig. 5.—Effect of  $\frac{1}{3}$  c.c. pituitary extract on cortical hemorrhage. Lettering same as before.

Attention may be directed to the fact that this statement in no way denies the ability of pituitary extract to constrict the renal vessels, although it must be admitted that no conclusive evidence of such action has yet been brought forward. We are concerned here, as in the case of adrenalin, not with the question of a drug's ability to constrict the renal vessels, but whether the local constriction is sufficient to counteract or overpower the rise of blood-pressure occasioned. This the constriction caused by pituitary extract is unable to do.

#### *Summary*

1 Pituitary extract is inferior to adrenalin as a hemostatic in renal hemorrhage. If too large an injection be not given, venous and cortical

<sup>4</sup> Magnus and Schäfer. *Jour. Physiol.*, 1901, **xxvii**, Proc. Phys. Soc., London, p. 9.

hemorrhages continue to decrease naturally from coagulation of the blood, while arterial hemorrhages are but rarely increased.

2 Pituitary extract does not constrict the renal vessels sufficiently to counteract the general rise in blood-pressure.

3 Since pituitary extract in intravenous doses of 0.5 to 1 c.c. does not actively increase hemorrhages, it may be used in those cases in which hemorrhage has ceased, but a permanent elevation of the blood-pressure is demanded.

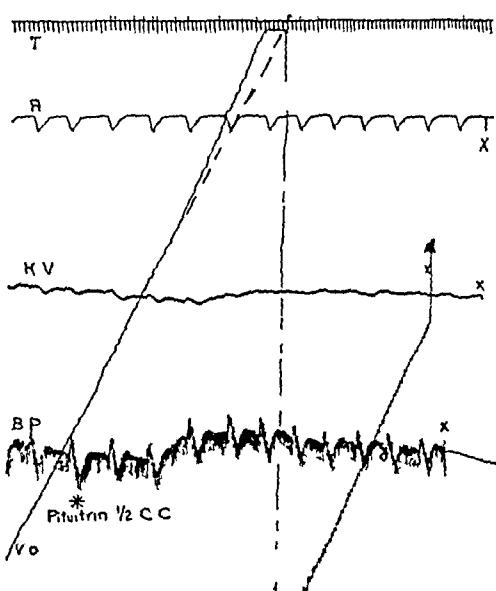


Fig. 6.—Effect of 0.5 c.c. pituitary extract, administered at point indicated by star on flow of blood from left renal vein (V O), on volume of right kidney (K V), on blood pressure (B P) and on respiration (R). T, time in seconds.

#### V THE INFLUENCE OF ERGOT (ERGOTOXIN)

The evidently beneficial results from the use of ergot in uterine hemorrhages has given the drug a reputation of being efficacious, through its vasoconstricting power, in checking the bleeding from other organs. Such therapy is entirely empirical, however, for it is now known that its beneficial influence in uterine hemorrhage results from its action on the muscle of that organ rather than on the blood-vessels.

It has been with great reserve and caution that clinicians have transferred the vascular actions of ergot, as determined by animal experiments, to patients. This attitude has apparently been just, for it has always been difficult to harmonize what seemed definite evidence of its vasoconstricting ability, with the great fall in pressure, followed at the most by a feeble rise, when an intravenous dose of ergot was given to animals.<sup>5</sup>

<sup>5</sup> Sollmann, T., and Brown, E. D. *Jour Am Med Assn*, 1905, **lv**, 234.

This state of affairs has largely been due to the fact that, by the intravenous administration of crude ergot preparations, so many substances are introduced which act to neutralize and complicate the effect of its constricting principle, whereas many of these accessory substances either are not absorbed or are neutralized or destroyed when the drug is given subcutaneously. This accounts for the fact that intramuscular injections induce only a rise and never a fall of pressure.

Although ergot when intramuscularly given is clearly a pressure-raising drug and, in this respect, may be deemed of advantage in hemorrhage, proof is still wanting that it is capable of producing a constriction of the renal vessels out of proportion to the rise of pressure induced, a condition necessary in order to prove a hemostatic. This question was investigated in this research.

The rate of absorption of ergot preparations from intramuscular tissue is so slow as to present an obvious difficulty in determining its effect on the bleeding. The difficulty is obviated, however, by the intravenous use of ergotoxin, which is generally admitted to be at least one of the active principles of ergot. The ergotoxin phosphate used in these experiments was kindly prepared by Dr. Brauns according to the method of Kraft.<sup>6</sup> A stock solution was made by dissolving the ergotoxin phosphate in distilled water slightly acidulated with phosphoric acid.

#### *Effects on Blood-Pressure and Respiration*

The effects produced by ergotoxin during hemorrhages were determined in thirty experiments. One-tenth milligram was found sufficient as a first dose to elevate the blood-pressure from 10 to 25 mm., while as much as 0.5 to 2 mg. were necessary to induce a similar rise on second injection. This fact unfortunately interdicts the use of more than a single injection in hemorrhages, for the larger doses markedly depress the respiratory centers. After such an injection the breathing becomes slower and shallower, or takes on a characteristic Cheyne-Stokes type, followed by respiratory failure. Variations in the blood pressure also occur which at first suggest a rhythmic vasomotor action (Traube-Hering waves), but which, in some cases at least, are evidently caused by the mechanical effects of the respiratory rhythm (Fig. 7). The resistance to subsequent hemorrhage is also decreased, as is shown by the fact that dogs stand the loss of a smaller quantity of their blood after a previous dose of ergotoxin.

The pressure-raising ability of ergot wanes as the loss of blood increases. In these experiments it was found that a dose of ergotoxin, causing a great and prolonged rise of pressure in a normal animal, created only a temporary rise or none at all in a bleeding one, the effect



Fig. 7—Segment of record showing Cheyne Stokes breathing induced by ergotoxin and the mechanical effect of this breathing on blood-pressure

being determined by the extent of hemorrhage (Fig. 8). Sollmann<sup>5</sup> has shown similarly that the pressure-lowering ability of crude ergot preparations depended on the volume of blood lost.

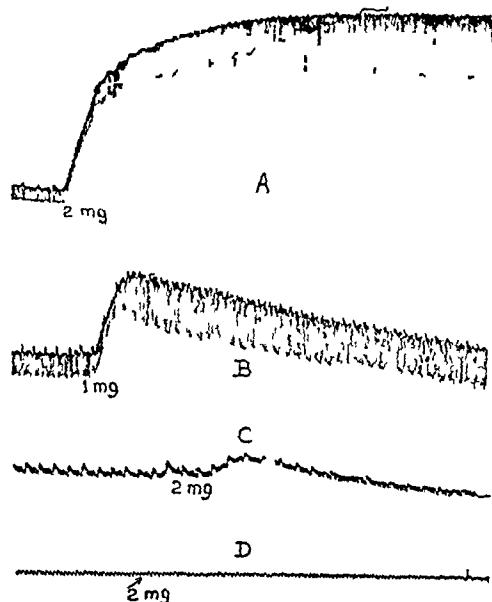


Fig. 8—Effect of hemorrhage on the blood-pressure reaction following an injection of ergotoxin. A, 2 mg ergotoxin on normal dog. B, 1 mg ergotoxin after a hemorrhage equal to 2 per cent body weight. C, 2 mg ergotoxin after a hemorrhage equal to 3.5 per cent body weight. D, 2 mg ergotoxin after a hemorrhage equal to 4.5 per cent body weight.

From these considerations it becomes clear that the pressure-raising value of ergot is limited to the early stages of hemorrhage, and that it

does not improve the respiratory center as adrenalin and pituitary extract do. In fact, the respiratory center is depressed unless small doses are used.

#### *Hemostatic Value in Renal Hemorrhages*

The results of thirty cases of renal hemorrhages show that ergotoxin tends, when factors aside from the vascular ones are excluded, to increase all forms of renal hemorrhage. The flow from a renal vein also becomes greater and oncometer records show an increase in the volume of the kidney (Fig. 9).

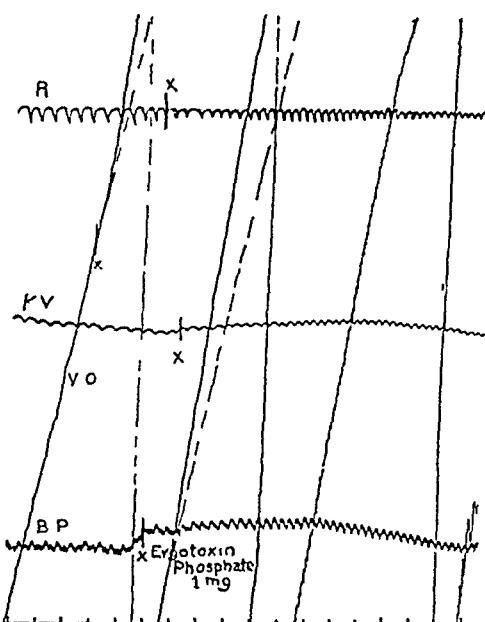


Fig. 9.—Effect of ergotoxin phosphate (1 mg administered at x) on the flow of blood from right renal vein (V O), on volume of left kidney (K V), on blood-pressure (B P) and respiration (R).

In about 20 per cent of cortical and 25 per cent of venous hemorrhages the course remained unaltered or the hemorrhages kept on decreasing if already tending that way. There is not the least evidence, however, that the ergotoxin contributed in any way to the decrease in these cases.

#### *The Effect of Adrenalin After Ergot*

The observation was quite accidentally made that, after previously testing ergotoxin, adrenalin no longer caused a favorable decrease in renal hemorrhages, but actually increased them. Further experiments also showed that the flow of non-coagulating blood from a renal vein and the size of the kidney were also increased. This observation is of practical importance in showing that an injection of adrenalin should never be

made when ergot has previously been used, for the favorable effect of the adrenalin is then converted into one distinctly unfavorable.

In 1906 Dale announced that ergot principles were capable of converting the usual constrictor action of adrenalin into one of dilatation, a reaction which characterized itself in the cat as a fall in blood-pressure. This "vasomotor reversal" has not been so successfully demonstrated in the dog, for even after large doses of ergot the pressure usually continues to rise after adrenalin. These experiments give undoubted proof that a reversal of the adrenalin action occurs in the kidney after relatively small doses. As shown in Figure 10, however, this reversal of vascular action

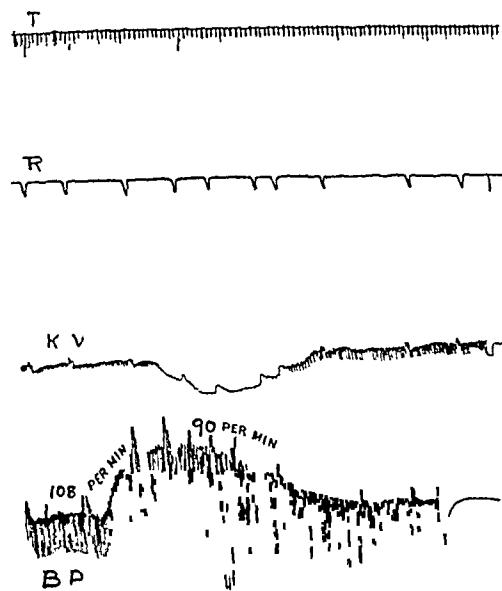


Fig. 10A

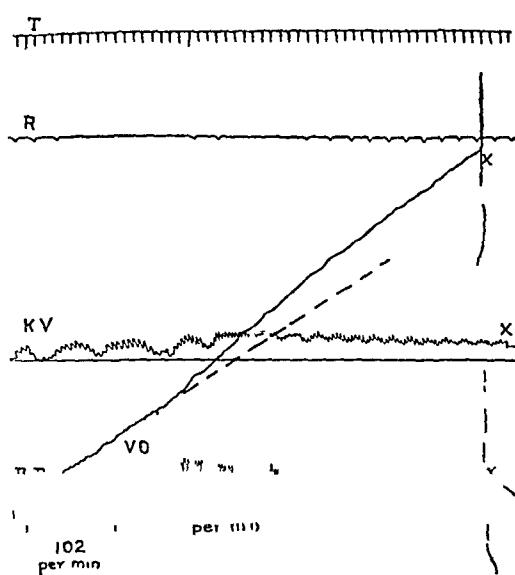


Fig. 10B

Fig. 10.—Two records contrasting the action of adrenalin (0.04 mg administered at \*) on the volume of the kidney (K V), on venous outflow (V O) and heart rate, (A) before and (B) after use of ergotoxin.

does not mirror itself in the blood-pressure records, because the normal slowing of the heart by adrenalin is changed to an acceleration sufficient to overpower the dilating peripheral vessels. In other words, ergot not only reverses the action of adrenalin on the blood-vessels, but also reverses its action on the heart of the dog.

#### SUMMARY OF ADRENALIN ACTION

	Before Ergot	After Ergot
Blood-pressure	Rose	Rose less
Kidney volume	Decreased	Increased
Renal hemorrhage	Decreased	Increased
Heart rate	Slowed	Accelerated

*Conclusions*

Ergotoxin cannot be looked on as a drug of value in renal hemorrhages, for the following reasons.

1 It causes a permanent elevation of pressure only when the loss of blood has been relatively small, thus restricting its use to the early part of a hemorrhage

2. Unless small doses are employed it depresses the respiratory center instead of stimulating it

3 Ergot interferes with the subsequent beneficial effects of adrenalin

4 Ergot is not a hemostatic in renal hemorrhages. The local constriction is not sufficient to counterbalance the rise in blood-pressure, consequently renal hemorrhages tend to increase unless some subsidiary factor prevents this

## VI GENERAL SUMMARY

That drug is of the greatest therapeutic value which is capable of decreasing the bleeding at the same time that it creates a better blood-supply to the brain. The activity of the respiratory center furnishes an indication of its value in this capacity.

Of the drugs studied in renal hemorrhages adrenalin alone fulfills these requirements. Nitrites decrease bleeding satisfactorily, but often dangerously diminish the blood-supply to the brain. Pituitary extract elevates the pressure and improves respiratory activity, but is not a hemostatic. Ergotoxin is not a hemostatic, and the beneficial action that the blood-pressure rise should occasion is counteracted by the depressing influence on the respiratory center.

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# THE RELATION OF TYPHUS FEVER (TABARDILLO) TO ROCKY MOUNTAIN SPOTTED FEVER<sup>\*</sup>

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AND

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One who has seen Rocky Mountain spotted fever cannot fail to be impressed with certain points of similarity which the disease shows to typhus fever (*typhus exanthematicus*), basing the comparison on the descriptions of typhus which are given in standard treatises. These descriptions refer to typhus as it occurs in certain European and Asiatic countries. It seemed desirable, therefore, to study their relationship, along clinical, anatomical and immunological lines, at least in certain essential respects.

Our observations concern tabardillo, the typhus fever of the great Mexican plateau, which differs in some important respects from European typhus, according to the opinion of those who have studied the disease minutely (e.g., Jose Terres, in "*Etiologia del Tabardillo*"). It is stated that the typhus of Mexico has a more gradual onset and defervescence than that of the old world. These are both said to be very sudden in the latter, whereas in the former the fever rises gradually for three or four days during the onset, and defervescence occupies a similar period. The two diseases should again be subjected to a close comparative study in these respects.

A peculiar topographic distinction exists between the two, in that the typhus of Mexico is limited to the plateau and is said not to occur at or near sea-level, that is to say, it does not occur in the so-called "hot country" of Mexico. European typhus, on the other hand, finds its home to a large extent at sea-level. In view of the fact, however, that typhus, the world over, is a disease of temperate and cool climates, the discrepancy mentioned is only an apparent one, it loses significance when we consider that the climate of the great Mexican plateau is a temperate one, while that of the sea coast towns is warm or torrid, in which general experience indicates that typhus is not able to prevail.

\* From the Department of Pathology (University of Chicago), and the Memorial Institute for Infectious Diseases, Chicago.

## COMPARISON OF SPOTTED FEVER AND TYPHUS FEVER

*Eruption*—In both spotted fever and typhus fever a macular or slightly elevated roseolai eruption occurs, which commonly becomes petechial, and which appears at about the same time in both diseases, but perhaps a little earlier in spotted fever. In typhus it is first seen at about five days after the beginning of the fever, and in spotted fever on from the second to the fifth day. In both diseases small hemorrhages (petechiae) may occur either in the preexisting rose-colored spots or at points in the skin which were hitherto uninvolved. In the former case a petechia with a congested zone is formed, and in the latter the aieola is absent. The hemorrhages appear to occur earlier and with greater regularity in tabardillo than in spotted fever, although this phenomenon is subject to great variations in the latter disease.<sup>1</sup> In some instances of spotted fever sharply marked petechiae do not occur at all, while the opposite extreme occasionally is encountered, the petechiae appearing before a roseolai eruption is definitely recognizable. Although petechiae do not occur invariably in typhus, they would seem to be more constant than in spotted fever. In both diseases the "spots" show a certain slight degree of induration, this is quite marked in some cases of spotted fever.

There seems to be a characteristic difference in the regions of the body first involved. In spotted fever the spots first appear on the forearm and lower leg in a large percentage of the cases, whereas in typhus they are first seen on the abdomen and sides of the chest. There are variations, however, in the sequence of distribution in spotted fever, so that it is doubtful if this point is of great distinctive value.

In both infections the distribution in the end is a very general one, including the face, palms and soles. It would seem that the involvement of the palms and soles is more prominent in spotted fever than in typhus. As regards profuseness there is no essential difference.

*Gangrene*—In the spotted fever of Idaho, gangrene of the foreskin and scrotum, the tonsils and faucial pillars occurs not infrequently, this is not seen so frequently in the more severe type which prevails in Montana. In typhus, the toes, feet and lower leg occasionally become gangrenous, and extensive bedsores are rather frequent.

*Changes in Internal Organs*—In spotted fever the spleen is habitually enlarged. This can be determined clinically in practically all cases, and at autopsy the mass of the spleen is sometimes three or four times that of the normal organ. In Mexican typhus it shows little enlargement.

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<sup>1</sup> See the Fourth Biennial Report of the State Board of Health of Montana, 1907 8, p 137

and this can rarely be detected clinically. In one autopsy it was of normal size, in another it was slightly enlarged, but cirrhosis of the liver was also present. In both diseases it is of rather firm consistence, in no way resembling the spleen of typhoid fever.

In spotted fever the lymph-glands are distinctly but moderately enlarged, in typhus they are smaller, but probably a little larger than normal. They show more congestion in spotted fever.

In typhus the meninges almost constantly show a great deal of congestion and edema at autopsy so that it has sometimes been spoken of as meningeal typhus. This condition also is stated as being present in European typhus, but perhaps not as constantly as in that of Mexico. It is a minor finding in spotted fever.

At autopsy the right heart and venous system show more engorgement in spotted fever than in typhus and this corresponds also with the clinical appearances of the two diseases.

Other organs appear uninvolved in typhus and spotted fever, except for the presence of occasional complicating infections, particularly pneumonia.

There appears to be nothing unique therefore, as to anatomical changes, in either disease.

*Fever*.—In typhus the fever begins and ends with a good deal of abruptness. Two or three days may be required after onset before it reaches its high point, and an equal period is occupied in defervescence. On the other hand, the temperature in spotted fever may not reach its maximum until a week or more after onset, and defervescence may occupy a week or ten days. This is one of the marked differences between the two diseases.

*Pulse*.—In the early part of the course, and in mild cases throughout, the pulse in spotted fever (90-110) is slower than in typhus (110-120) under similar conditions. In both it rises to 140 or more preceding a fatal issue.

*Mental Effects*.—Stupefaction, or a low nervous delirium is common to both.

*Convalescence*.—This varies with the severity of the infection in both diseases, but on the whole it is much slower in spotted fever than in typhus. This may be due in part to the longer duration of spotted fever.

*Duration*.—The "crisis" in typhus usually occurs on from the tenth to the fourteenth day, although some cases may cover a period of three weeks. Patients suffering from spotted fever are rarely convalescent until the end of the third week, and they commonly remain bedfast for from four to six weeks.

*Character of the Infections*—In both, the condition is that of a systemic blood infection (and presumably lymph infection), without the critical involvement of particular organs. These points are brought out by the findings at autopsy, and by the result of inoculations with the blood of patients. Blood from spotted fever patients is always infective for the guinea-pig, monkey and certain other animals. In a number of instances reported in the literature, the blood of typhus patients apparently has produced the disease when injected into other human beings, and Nicolle's infection of the chimpanzee was done by the same means, this concerns European typhus. The experiments with Mexican typhus, reported recently by Anderson and Goldberger and by ourselves, also show that the latter is a generalized infection.

*Transmission*—Spotted fever is not contagious, and the evidence indicates that the same is true of typhus. The former is transmitted by the bites of certain species of ticks, while presumably the latter is carried by the body louse (*Pediculus vestimenti*). It is probable, therefore, that they have the feature of insect transmission in common, but two altogether different types of insects are concerned.

It is a peculiar fact that the conception of contagiousness has adhered to typhus up to and including the present time. Yet, in view of the facts that typhus, when endemic in a city, remains rather strictly segregated in the poor quarters, and that more or less intimate contact is required for transmission, it is manifest that contagiousness, if present at all, must be of a peculiar character and of a low grade. Typhus has never overwhelmed a whole city as smallpox did again and again in former times. In recent years, however, belief in the theory of insect transmission of typhus has extended widely, as affording a better explanation of the epidemiologic features of the disease. Thus the flea and bedbug have repeatedly been mentioned in relation to European typhus, and Gaviño and others have called attention to the possibility of insect transmission in Mexico, without indicating the probable species, however.

The recent experiments of Nicolle in transmitting European (rather Asiatic) typhus from monkey to monkey by means of the body louse affords a good working basis for clearing up the natural means of transmission.

Our own experiments with the louse, which have been successful in a measure, will be reported at a future date.

*Susceptibility of Animals*—Aside from the discrepancies between spotted fever and typhus which were mentioned above, a striking difference is found in the susceptibility of animals to the two diseases. As regards European typhus the literature contains numerous references to

attempts to infect the guinea-pig and other ordinary animals of experimentation by the injection of blood from patients, the results being uniformly negative. Likewise, in extensive experimentation with the typhus of Mexico, Director Gavíño of the Bacteriologic Institute of Mexico City, and his assistants, failed to produce any evidence of infection in guinea-pigs, rabbits, white rats and mice, by the subcutaneous and intravenous injection of blood from human patients, the blood being taken at different periods of the disease.<sup>2</sup> Similarly, and in substantiation of Dr. Gavíño's results, Anderson and Goldberger reported their failure to infect the guinea-pig by the injection of virulent typhus blood.<sup>3</sup>

These results seem so conclusive that we decided not to repeat the experiments.

In contrast to this condition, a fairly large experience has shown that spotted fever may be transmitted to the guinea-pig invariably, by the subcutaneous or intraperitoneal injection of virulent blood, provided no serious error in technic has been made.<sup>4</sup>

The difference in the susceptibility of the guinea-pig to the two diseases must be taken as showing definitely that typhus and spotted fever are not identical. It might also stand as sufficient reason for concluding that they could not be even related infections, were it not for the fact that there are two types of spotted fever, one of which appears to be less virulent for the guinea-pig than the other. The spotted fever of western Montana, which represents the more virulent type, can be maintained indefinitely in the guinea-pig by passage from one animal to the other. On the other hand, it has been impossible, on three occasions, by the use of the same method, to keep alive in the guinea-pig the mild type of the disease which prevails in southern Idaho. It "died out" after from two to ten passages, presumably because of a loss of virulence for the guinea-pig. Yet, other experiments, particularly that of agglutination, as performed with the bacilli found in the eggs of the tick, indicate that the two types which occur in Montana and Idaho, respectively, are identical or closely related.

<sup>2</sup> General reference to these experiments is made in an article by Dr. Gavíño in *Gaceta Médica de México*, 1906, 1, 218. They are also cited elsewhere in the same publication, the exact references not being before us at this moment.

<sup>3</sup> Anderson and Goldberger. The Relation of Rocky Mountain Spotted Fever to the Typhus Fever of Mexico—A Preliminary Note, Pub. Health Rep., 1909, xxiv, 1861.

<sup>4</sup> It is important that the blood injected should be drawn rather early in the disease, and that the quantity injected should not be too large, dilution with salt solution favors infection. This has been referred to in previous articles by one of us.

As bearing on typhus fever, this condition raises the question as to whether there may be a third type of infection (typhus fever) which is related to spotted fever, but which differs from it not only in certain important clinical respects, but also in possessing even a less degree of virulence for the guinea-pig than the mild spotted fever referred to above. In other words, may typhus fever have a group relationship to the spotted fever of the Rocky Mountains?

#### IMMUNIZATION EXPERIMENTS

We have resorted to protective and agglutination experiments in order to obtain more conclusive data regarding this point. The experiments may be reported briefly.

One attack of spotted fever, or of typhus renders the individual immune to further attacks of the same disease. This acquired immunity in spotted fever is characterized by the formation of protective antibodies, which appear in the blood, and which can be demonstrated by experiments on the guinea-pig. From 0.1 to 0.2 c.c. of serum from the immune guinea-pig protects against 1.0 c.c. of virulent blood, representing from 200 to 1,000 pathogenic doses. From 0.3 to 0.5 c.c. of serum from the convalescent human patient were required to exert the same protective effect in two experiments. If typhus were identical with spotted fever the serum from typhus convalescents should exert a similar protective effect against spotted fever, or, if typhus occupied a "group relationship" to spotted fever, this might be manifested by a certain (perhaps low) degree of protective effect against spotted fever, on the part of serum from typhus convalescents.

As will appear, the experiments to be reported do not disclose with certainty the relationship which has been suggested, and possibly they are of such value that a close relationship is actually disproved.

The immune typhus serums were all taken from patients whose course we had observed in the General Hospital (Mexico City), and in whom the diagnosis of typhus seemed to be without doubt. Their histories will not be recited. The blood was drawn on from the seventh to the tenth day after the subsidence of fever, after the patients had left their beds, and the serum obtained by defibrillation and centrifugation, or by spontaneous clotting.

Three sets of controls were utilized: first, the protective power of normal human serum as compared with that from the typhus convalescents; second, the tests of the toxicity of human serum alone for the guinea-pig; third, inoculations to determine approximately the strength (quantity or virulence) of the spotted fever virus used in each experiment.

## THE PROTECTIVE POWER OF CONValescent TYPNUS SERUM AGAINST SPOTTED FEVER

			Guinea-pig Inoculation, days	Inoculation, days of fever	Duration, days of fever	Result	Remarks
<b>EXPERIMENT 1</b>							
Case 2, R	2.0	1.0	2644	3	9	Death	Autopsy spotted fever
	1.0	1.0	2645	3	13	Death	Autopsy spotted fever
Controls	0.5	1.0	2646	3	14	Death	Autopsy spotted fever
	2.0	1.0	2647	3	6	Death	Autopsy spotted fever
Controls with virus	0.5	1.0	2648	3	11	Recovery	
	0.1	0.1	2649	3	8	Death	Autopsy spotted fever
To determine toxicity of serum	0.05	0.05	2650	4	Killed on sixth day of fever		
	0.01	0.01	2651	3	Killed on sixth day of fever		
	2.0	0	2652	4	8	Death	Autopsy spotted fever
	2.0	0	2653			No fever	Remained well
	2.0	0	2654				
	2.0	0	2655				
<b>EXPERIMENT 2</b>							
Case 1 M—1	3.0	0.5	2669	5	9	Recovery	
Controls	2.0	0.5	2670	4	10	Recovery	
Controls with virus	2.0	0.5	2671	4	8	Death	Autopsy spotted fever
	3.0	0.5	2672	2-3	14-15	Death	Autopsy spotted fever
To test toxicity of serum	3.0	0.05	2673	3	Killed on 7th day		
	2.0	0.01	2674	4	Recovery		
	2.0	0.01	2675	6	10	Death	Autopsy spotted fever
	2.0	0	2676	7	7	Accidental death	
	2.0	0	2677	7	Not sick		
	2.0	0	2677				
<b>EXPERIMENT 3</b>							
Case 17 P—1	3.0	0.1	1	4	6	Death	Autopsy spotted fever
Controls	2.0	0.1	2	6	6	Recovery	
Controls with virus	1.0	0.1	3	5	7	Death	Autopsy spotted fever
	3.0	0.1	4	7	7	Death	Autopsy spotted fever
To test toxicity of serum	3.0	0.005	5	4	7	Death	Autopsy spotted fever
	2.0	0	2677				
	2.0	0	2677				
<b>EXPERIMENT 4</b>							
Case 24 E—1	2.0	0.01	9	✓			
Controls	1.0	0.01	10	✗			
Control with virus	2.0	0.01	8	✓	6	Death	Autopsy spotted fever
	1.0	0.01	11	✗	6	Slight fever, resulting in vaccination as shown by immunity test given 2 weeks later	
Control with virus	0.005	0.005	12	✗	6	Death	Autopsy spotted fever
						Slight fever, resulting in vaccination as shown by immunity test given 2 weeks later	
						shown by immunity test given 2 weeks later	

ment. The virus was that represented in the defibrinated blood of the infected guinea-pig on the third day of its fever.

The virus and serums were mixed, and injected intraperitoneally as soon as possible thereafter, the syringe was washed with salt solution and the washings injected, in order to render the experiments as nearly quantitative as possible.

It will be noted that, as the experiments progressed, the proportion of convalescent typhus serum to spotted fever virus increased from  $\frac{1}{2}$  to 1 (Experiment 1), to 200 to 1 (Experiment 4).

One would expect to find evidence of a protective power in absolute prevention of infection, or, if present to a low degree, in a prolongation of the incubation period above that of the controls, in a shorter course of fever, or in recovery as compared with the death of the controls. Three animals in the series, 9a, 11a and 12a, suffered such light attacks that they could not be recognized positively by the temperatures exhibited, the result being determined only by immunity tests which were administered later. The accompanying table gives the outlines of the experiments.

Analysis of the table shows with reasonable clearness that the typhus serum exerts no more protective effect than does normal serum. Interest centers chiefly in Experiment 4, in which the dose of virus was approximately twice the minimum infective quantity. The immune typhus serum showed a certain degree of protection in doses of 10 and 20 c.c., but on the other hand, 10 c.c. of normal serum showed the same degree of protective power. We may consider that the dose of virus used was so low that very slight influences were able to determine the occurrence or non-occurrence of infection.

Another experiment also indicates that an attack of typhus fever in the monkey does not protect the animal against a subsequent infection of spotted fever virus. Monkey 11 was inoculated with typhus by means of blood drawn from Monkey 7 on the eighth day of the latter's fever. After an incubation period of nine or ten days the temperature of No. 11 rose, and the animal passed through a course of fever similar to that which has appeared in other animals inoculated with virulent typhus blood. Twenty-seven days after the inoculation and after recovery was complete a second injection of typhus virus, consisting of 5 c.c. of blood from a human patient, was given to No. 11, in order to determine immunity or non-immunity to the disease. No fever resulted over a period of eighteen days. A control monkey (No. 21) which received a similar injection passed through a course of fever resembling that of typhus. We may, therefore, consider that No. 11 had been infected by its first injection of typhus virus, and that this resulted in immunity to the disease.

In order to test the animal's immunity to spotted fever, after the lapse of some days it was injected intraperitoneally with 3 c.c. of defibrinated blood from the infected guinea-pig, drawn on the third day of the latter's fever. The blood was diluted to 6 c.c. by means of salt solution before being injected. The following course of fever developed

	A.M.	P.M.
March 13	102	102 4
March 14	102 6	103 3
March 15	102	102 4
March 16	103	104 6
March 17	104 7	105 6
March 18	103 1	106 4
March 19	104 6	106 7
March 20	104	105 6
March 21	105 8	106 8
March 22	105	106 6
March 23	101 4	104 1
March 24	99	103

On March 23 and 24 an extensive hemorrhagic eruption developed on the extremities, tail and back, such as has occurred previously in spotted fever in the monkey.

As a control a guinea-pig inoculated with 1 c.c. of the same virus developed a typical course of spotted fever, as did a second guinea-pig inoculated with the blood of No. 11.

This experiment indicates, therefore, that an attack of typhus in the monkey does not render him immune to spotted fever, although it does protect him against infection from a second injection of virulent typhus virus.

#### AGGLUTINATION EXPERIMENTS

As reported previously by one of us, immune spotted fever serum agglutinates to a marked degree a bacillus which occurs in the eggs of ticks which act as carriers of the disease. The agglutination is specific, in that normal serums do not have this agglutinating effect, or have it to a very low degree, and this, among other reasons, is taken to indicate that the organism bears a causal relation to spotted fever.

This reaction was utilized as a means of determining a possible relation between spotted and typhus fevers. As in previous experiments, an emulsion of the bacilli was obtained by crushing a sufficient number of eggs in a small quantity of salt solution, and with this emulsion the microscopic agglutination test was performed with various dilutions of serum from convalescent typhus patients. Duplicate preparations with normal human serum were made, and, in addition, with immune spotted fever serum from the guinea-pig in order to make certain of the character of the bacilli.

In the case of the immune spotted fever serum the agglutination was marked or complete in three experiments up to a dilution of 1 in 500. Numerous experiments have shown that serum from normal guinea-pigs agglutinates only in dilutions of 1-10 to 1-20. Normal human serum caused slight agglutination at low dilutions (1 in 10 and 1 in 20). The serum of typhus convalescents, drawn within a week to ten days after the subsidence of fever, had approximately the same agglutinating power as the normal serum in two experiments, while in a third it reached a dilution of 1 in 40. Even in this case, however, the agglutination was not complete at this dilution.

#### SUMMARY AND CONCLUSIONS

The serum of typhus convalescents, drawn within a week to ten days after the subsidence of fever, exerts no more protective effect against spotted fever than normal serum does.

Also such serums show little or no more agglutinating effect for the bacilli which appear to be associated with spotted fever than do normal serums.

A monkey which had been rendered immune to typhus was not immune to spotted fever.

These experiments go to substantiate the clinical evidence and that obtained by animal inoculations, that spotted fever and typhus fever are not identical, and they seem also to indicate that the organisms of the two diseases are not closely related biologically, whatever the morphologic conditions may be.

The fact also that the serum of a disease (typhus) which is roughly similar to spotted fever, has no unusual agglutinating power for the bacilli mentioned, as compared with the high agglutinating power of immune spotted fever serum, supports the contention that this bacillus bears a causal relation to spotted fever.

We are indebted to Director Gavirio of the Bacteriologic Institute and to his assistant, Dr. Guillard, for the use of their laboratory and for numerous courtesies; to Dr. Escalona of the General Hospital for his cooperation and to Mr. J. J. Moore of the University of Chicago for assistance in the experiments.

## PERFORATING ULCER OF THE FOOT IN ALCOHOLIC NEURITIS

### REPORT OF A CASE

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The occurrence of perforating ulcer of the foot with certain disorders of the nervous system has long been recognized. The first description was given by Nélaton in 1852. Since that time the condition has been described in connection with a number of nervous conditions. It is frequent in diseases of the spinal cord, such as tabes and syringomyelia, and has been noted in spina bifida, diseases of the conus medullaris, diabetes and alcoholism. Injuries to the sciatic and tibial, as well as tumors and local inflammatory disturbances of these nerves, have also caused this condition. It is frequent in the neuritis of leprosy. Its occurrence in multiple neuritis, aside from the form due to diabetes, is very infrequent. In the accessible literature I have not been able to find any record of its occurrence in alcoholic neuritis. Sonnenburg noted it in an alcoholic with anesthesia of the foot. Remak and Flatau,<sup>1</sup> writing in 1899, say "So scheinen Fälle von Alcoholneuritis mit Mal perforant nicht mitgetheilt zu sein, wenn auch die Möglichkeit dieses Vorkommen durchaus nicht bestritten werden soll."

*History.*—The patient was a white male, aged 37, with a negative family history. He denied syphilis. His work entailed a great deal of loss of sleep with irregular meals. Owing to a condition of his nervous system which had best be called a "constitutional neurasthenia," he was easily exhausted, and had tried all sorts of artificial means to keep up his strength. For some months prior to the onset of his trouble he had been using alcohol in the form of whisky in large quantities. For three months before the onset of his illness he had been taking not less than a quart a day. He continued to work and took very little food. He came under my observation in October, 1898. His illness had commenced gradually three months before this, with pains in the legs, followed by weakness and atrophy of the muscles, hyperesthesia and redness of the skin. About a month after the onset of the trouble in his legs the hands and arms also became involved. He had been under treatment for two months. At the time I first saw him he complained of great pain in the legs, particularly at night, hyperesthesia of the skin below the knee, and marked tenderness in the muscle groups of the legs and arms. He was unable to walk and could with great difficulty use his arms to feed himself.

<sup>1</sup> Nothnagel Specielle Pathologie und Therapie, Vienna, 1899 vi, Th III  
Abth III

*First Physical Examination*—This showed a poorly nourished man with gray hair. The mucous membranes were pale. He was lying in bed in the dorsal decubitus. The examination of the thoracic and abdominal organs showed nothing of note. The patient had no lymphatic enlargement, and no bladder or rectal disturbances. The nervous system showed no involvement of the cranial nerves. The pupils were equal and reacted to light directly and consensually and to accommodation. The upper extremity reflexes were elicited with difficulty. The abdominal and cremaster reflexes were very sluggish. The knee jerks, Achilles tendon reflexes and plantar reflexes were absent. There was marked weakness of the extensor and flexor groups of the wrist and fingers. This was most evident in the extensor groups, giving rise to the typical "wrist drop." There was great muscular atrophy and motor weakness of both lower extremities, the power of the flexors and extensors of the toes and feet being practically wanting. The quadriceps groups and flexor group of the back of the thigh showed a diminished motor power.

*Sensation*. There was marked hyperesthesia of the skin of the feet and legs. The pain and temperature sensation were practically wanting from below the knees and below the wrists in the upper extremities. The touch sensation of the upper extremities was also much diminished. Touch sensation in the lower extremities was much delayed and, except in the hyperesthetic areas, was almost wanting. The muscles of the calves and of the thigh were very tender on pressure. The nerves were tender, but no swelling could be made out on palpation.

*Course of Disease*—The patient's recovery was uninterrupted and he returned to his home in the spring. At this time he was able to walk with the assistance of two canes. In July of the present year, after considerable walking, he noticed that the skin over the distal ends of the third metatarsal bones of both feet was greatly thickened. Later the center of this area broke down, leaving a large ulcerated area. This extended in quite deeply and discharged a considerable quantity of pus. These ulcerated areas differed in no way from the perforating ulcers seen in tabes dorsalis. At first they were not very painful, but as the sensation improved the patient noticed that the pain increased. If he would keep perfectly still the pain would not be very marked. The ulcer on the left foot was much larger and deeper than the one on the right foot. At its maximum, it extended three quarters of an inch across, and in the deep fascia. As far as could be ascertained, there had been no involvement of the tendons or of the deeper structures. The skin surrounding these areas was anesthetic to pain, but, as the sensation continued to improve, the ulcers became very painful. The causation of these ulcers was of some interest. The patient had a flattening of the anterior arch of both feet, and the thickening had existed for some time prior to the onset of his neuritis. This thickening had occurred over the head of the third metatarsal bones, and is very commonly seen in cases of flattening of the anterior arch. The pressure caused by continued walking, with the lowered trophic condition due to the inflammation of the peripheral nerves, was probably responsible for the ulceration. As the neuritis improved the ulcers slowly healed.

*Second Physical Examination*—In November, 1908, the knee jerks, Achilles tendon reflexes, and plantar reflexes had returned. The sensation showed an absence of capability to distinguish the light touch of cotton and the light prick of a pin in the feet. The deep sensation, formerly absent, was now normal. The sensation of the legs was normal. The fact that sensation had not completely returned is in keeping with the studies of Head, as he has shown that as long as two years may elapse without the return of the fine or epicerotic sensation, and, in this instance, the sensory loss belongs to this type.

The case is of interest as showing how the flattening of the anterior arch, a condition which, under normal circumstances, only gave rise to great thickening of the skin, had, when the neuritis was added, produced typical perforating ulcers. As a rule, trophic ulcers occur at the points of pressure at the base of the great and little toes. This central point seems to be the next in frequency. It would be of interest to note whether this flattening of the anterior arch might not be an important factor in the localization of perforating ulcers in tabes and other conditions. Since the preceding portion of this was written, in fact, a case of tabes dorsalis has been observed in which perforating ulcers, involving the deep structures in this situation, were associated with flattening of the anterior arches.

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## THE INFLUENCE OF SCOPOLAMIN-MORPHIN NARCOSIS ON METABOLISM

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During the course of some studies of metabolism it was desired to bring about a moderate grade of anesthesia in order that a diagnostic lumbar puncture might be made possible, and for this purpose a mixture of scopolamin (hyoscine), hydrobromate and morphin (sulphate) was given subcutaneously a short time before the operations were carried out.<sup>1</sup> It is stated<sup>2</sup> that morphin and several of its derivatives when given in therapeutic doses will cause no alteration in the respiratory metabolism, while conclusions concerning the protein metabolism are at variance, some observers having found an increase and others a decrease in the intensity. In either case the variation seems to have been quite slight. With atropin and several of its congeners, however, a somewhat more definite result seems to have been obtained. De Stella,<sup>3</sup> after long-continued small doses of scopolamin, noted in four experiments on rabbits and dogs that there occurred a decrease in not only the volume of the urine, but also in the content of nitrogen, phosphorus and chlorine. These experiments do not seem to be entirely conclusive, and it was determined to employ the drugs as usual and to keep watch for any effect on the metabolic functions.

The accompanying table picturing that portion of the investigation particularly related to the administration of the drugs is composed of the results obtained from the observation of five individuals, the first four of whom were subjects of undoubted paresis. The fifth was a healthy man, 23 years of age, employed as a nurse, who willingly offered his services for experimentation. The histories of the patients are not of importance in this consideration with the exception that in the two cases (those of P. L. F. and R. B. S.) scopolamin-morphin had been given almost daily.

\* From the Clinical Laboratory of the Sheppard and Enoch Pratt Hospital.

<sup>1</sup> In order to perform a lumbar puncture for the purpose of diagnosis in these patients it is desirable and generally necessary to administer some sedative medicine to allay the attacks of motor restlessness and irritability to which persons with general paresis are so frequently subject. The effects of the drugs thus administered for diagnostic and therapeutics measures are recorded here in so far as the metabolic functions are concerned.

<sup>2</sup> Von Noorden Pathologie des Stoffwechsels, ed 2, 1907, II, 775.

<sup>3</sup> De Stella Ibid., 1907, II, 807.

TABLE SHOWING EFFECT OF SCOPOLAMIN AND MORPHIN ON METABOLISM

Date	In c.c.	Sp Gr	Total	Urea			Ammonia			Nitrogen			Uric Acid			Rest			Total			Neutral			Sulphur			Inorganic			Etheral			Chlorine			Phosphorus			Remarks		
				Gm	%	Gm	Gm	%	Gm	Gm	%	Gm	%	Gm	%	Gm	%	Gm	%	Gm	%	Gm	%	Gm	%	Gm	%	Gm	%	Gm	%	Gm	%	Gm	%							
5/10	2300	1015	12.10				0.87	7.13	0.10	3.27	0.07	0.57							2.25	0.20	8.88	1.85	82.14	0.20	8.88	8.16	2.48	R N II—Pancytis														
5/20	1510	1019	10.19				0.61	5.73	0.45	1.23	0.10	0.90							2.21	0.20	9.00	1.88	81.60	0.13	5.85	10.03	2.26	Hycosin, gr 1/75, morphin, gr 1/4 at 2.00 p.m.														
5/21	1000	1026	10.71				0.18	1.46	0.39	3.03	0.10	0.93							3.70	2.77	0.32	11.55	2.15	88.45	0.00	0.00	15.16	2.93	Hycosin, gr 1/75, morphin, gr 1/4 at 2.00 p.m.													
5/22	3120	1024	12.84	10.13	80.31	1.19	11.17	0.38	2.93	0.06	0.42	0.48							3.02	0.25	8.28	2.61	87.38	0.13	1.31	11.07	3.73	P L F—Pancytis, Hycosin gr 1/100, morphin, gr 1/4 Hycosin, gr 1/75, morphin, gr 1/4 at 1.30 p.m.														
5/19	2050	1021	15.21				0.61	4.16	0.50	3.21	0.15	0.98							2.17	3.18	0.33	10.36	2.66	83.52	0.19	5.97	7.56	1.02	Hycosin, gr 1/100, morphin, gr 1/4 at 1.45 a.m.													
5/20	1260	1028	14.64	12.56	85.11	0.69	1.69	0.52	3.54	0.16	1.09	0.51							2.99	0.28	9.35	2.57	85.84	0.11	1.68	7.18	3.38	Hycosin, gr 1/100, morphin, gr 1/4 at 1.45 a.m.														
5/21	920	1031	12.84				0.51	3.93	0.43	3.31	0.11	1.00							7.30	2.70	0.24	8.88	2.34	86.58	0.12	1.44	7.53	2.80	Hycosin, gr 1/100, morphin, gr 1/4 at 1.30 p.m.													
5/22	965	1029	13.14	11.13	84.59	0.53	1.03	0.38	2.89	0.11	1.06	0.96							7.90	3.57	0.27	7.56	3.06	85.71	0.24	6.72	12.74	4.40	E J D—Pancytis													
5/3	1990	1021	17.75	15.21	85.18	0.56	3.14	0.63	3.73	0.14	0.78	1.11							1.13	2.52	0.27	9.13	2.52	85.18	0.16	5.44	10.50	3.53	Hycosin, gr 1/75, morphin, gr 1/4 at 3.30 p.m.													
5/4	1500	1022	14.49	12.68	87.50	0.48	3.32	0.51	3.73	0.13	0.90	0.66							3.39	3.98	0.36	9.04	3.34	83.83	0.28	7.03	9.71	3.87	Hycosin, gr 1/75, morphin, gr 1/4 at 3.30 p.m.													
5/5	1675	1022	18.85	16.07	86.17	0.64	3.39	0.59	3.13	0.16	0.85	1.39							1.50	0.40	3.10	0.10	0.77	2.83	0.24	8.47	2.37	83.66	0.22	7.77	11.02	2.77	R B S—Pancytis									
5/17	1670	1019	12.90				0.58												2.75	2.67	0.29	10.85	2.25	83.15	0.13	4.86	11.34	2.67	Hycosin, gr 1/75, morphin, gr 1/4 at 3.00 p.m.													
5/18	1890	1018	13.47	12.01	89.11	0.59	1.38	0.43	3.19	0.07	0.52	0.37							3.11	0.01	0.37	0.65	5.95	2.40	0.19	7.92	2.08	86.65	0.13	5.41	7.20	2.16	Hycosin, gr 1/75, morphin, gr 1/4 at 12.30 a.m. and respiration during p.m.									
5/19	1110	1017	10.92	9.42	86.19	0.47	4.30	0.34	3.11	0.01	0.37	0.65							3.78	0.11	0.11	0.79	2.56	0.28	10.94	2.12	82.81	0.16	6.25	9.52	2.80											
5/20	1100	1021	13.99				0.53												3.03	0.78	4.43	0.11	0.80	2.29	13.08	3.47	0.12	12.04	2.86	82.24	0.20	5.69	8.80	4.73	R W—Normal—Nurse							
5/21	880	1040	17.49	13.74	78.47	0.53	0.52												0.06	0.78	1.57	0.13	0.76	1.50	0.39	11.07	2.88	82.29	0.23	6.63	9.08	4.61										
5/22	890	1040	16.98																0.67	3.37	0.93	4.72	0.16	0.73	1.14	0.46	11.06	3.45	83.23	0.23	5.57	9.21	5.24	Hycosin, gr 1/100 at 4.45 p.m.								
5/23	1043	1048																	0.28	2.66	0.51	4.73	0.08	0.78	2.17	0.22	9.96	1.79	82.67	0.16	7.21	4.47	2.29									

\* Three duplicate determinations

for months preceding these observations. The other two patients (R. N. H. and E. J. D.) had had only very occasional doses of these drugs, and none at all for several months past. During these observations it so happened that the scopolamin-morphin was given during two successive twenty-four hours, with the exception of the one patient (P. L. F.) to whom it was given daily to allay excitement and motor restlessness. The hour of giving the drugs, together with the amount, is indicated in the table.

The plan of the work and the analytical procedures employed have not differed essentially from those previously described as used in this laboratory.<sup>4</sup> A liquid diet (the Folin milk and egg diet) prepared in the laboratory was taken throughout each of these separate periods. The collection of the urine began on the fourth morning after beginning the diet. Patients were kept in bed during the period of observation and were constantly under the watch of special nurses. The nurse experimented on engaged in the usual routine duties of the ward, with the exception of the evening when he was given the scopolamin.

The tabulation of the results makes patent the influence of the narcotic mixture, and only a few general points call for further textual notice. The narcotic effect of the drugs was evidenced in a fairly uniform manner so that, with the exception of one patient (E. J. D.), in whom only a decided drowsiness ensued, a profound sleep of from four to five hours was produced. The nurse who received the scopolamin alone showed an entirely different train of symptoms, which will be more fully mentioned later. It may be seen at a glance that the two patients (R. N. H. and E. J. D.), who had not been more or less accustomed to the drugs by frequently repeated doses, show very sharply the action of a single dose in so far as the urine and its several constituents are concerned. In the first instance (R. N. H.) a definite drop in almost every urinary constituent is evident, and this is perhaps even better shown in the other patient (E. J. D.). Such daily variations of so extensive degree have not been noted in the cases of paresis similarly studied, in which the drugs have not been administered. In these two patients on the day following the scopolamin-morphin there is to be noted an increase in the various urinary bodies, which in general gives amounts that are slightly higher than those of similar bodies on the days before the drugs were given. This increase, however, is not enough to compensate fully for the reduction following the giving of the drugs.

<sup>4</sup> Barnes. A Study of the Metabolism of Two Atypical Cases Related to the Dementia Praecox Group, Am. Jour. of Insanity, 1909, Ixv, 593.

When one examines the figures obtained from the other two observations on the patients (P L F and R B S) it is found that the same regularity of variation in the amounts of the different urinary constituents is not present in relation to the time of the administration of the drugs. The first patient (P L F), during the four days of the observation, received in all six doses of the drug mixture, and, of these, three were given on the third day of the period (April 21). The second patient (R. B. S.) was given three doses in all during the entire period, and all of these during the twenty-four hours ending May 19. Although there is, in general, more irregularity shown in the influence of the drugs on the urinary secretions, there is one point which seems quite clearly shown in the table, that is, on those days during which three doses of the drugs were given there occurred a decrease in the excretion directly analogous to that which has been observed in the other two patients when only one dose was given, and, further, it is seen that this reduction is not so quickly recovered from, and that on the next day the amounts are still lower than might be expected. This is particularly true with the first patient (P L F) and is not so entirely unexpected in accordance with the other results here obtained, as he received more of the drugs. In the other case it is to be noted that the volume of the urine particularly remains low, whereas the other constituents show a definite tendency to resume former levels. The points above indicated in these two cases would seem to show that in individuals who have become accustomed to these drugs by frequently repeated doses given over a long period of time some form of tolerance is produced which makes necessary the use of larger quantities of the drugs in order to bring about conditions of metabolism which occur with smaller doses when given to individuals not possessing such resistance from custom.

In none of these four cases was there noticed any especially constant disturbance of the relative amounts of the various urinary constituents, although there is shown a slight tendency toward an unequal variation. This is seen in the slight elevation of the nitrogen, phosphorus and sulphur ratios.

The outward action of the scopolamin alone on the nurse was opposite to that of the scopolamin-morphin on the patients; instead of drowsiness or sopor, a distinct elevation of function was occasioned. This was evidenced by motor restlessness and activity within a few minutes; soon unsteadiness in walking and general confusion of psychic processes were easily determinable. Within half an hour after the injection was made the nurse was put to bed and there remained until the following morning. For the succeeding hour and a half after going to bed there was present a

condition not entirely dissimilar to a mild delirium during which a conglomeration of pseudohallucinatory experiences and incomplete delusions, largely resultant from disturbances within the scope of the visual apparatus, together with an uncertain ability in personal identification, occurred. By 9 o'clock nearly all of these symptoms had vanished, although sleep did not occur until 1 o'clock the next morning. The sole unpleasant result of the experiment was the thirst following the wearing away of the effect of the drug. The results of the urinary analysis for these twenty-four hours show an increase in output which is not less interesting than the extraordinary decrease of the following day.<sup>5</sup> These daily variations are far too extensive to be entirely accidental. With several other "normal" persons on whom similar studies of metabolism have been made in this laboratory no such results have been obtained. The ratios, which in the four patients showed some tendency to variability, were not affected in this experiment, except that on the last day they were somewhat lower than previously. In general, there was in this individual an effect almost the exact opposite of that produced by the drugs given the four patients. Instead of the initial drop there occurred an increase followed by a fall.

Can these apparently divergent results be brought into accord? In this connection it is necessary to bear in mind that all but one of the patients received sufficient of the two drugs to bring about a depression of activities whereas the nurse was given the scopolamin alone and this resulted in a state of mild excitement. Individual idiosyncrasy must be given due consideration and especially in this instance as the nurse reports that although he has had no experience with drugs, he is particularly susceptible to alcohol, and small quantities will produce effects quite similar to those here noted to have followed the administration of the scopolamin.

The most striking point thus far met is that with the patients there is a decreased output through the kidneys coincident with a varying grade of outwardly apparent depression of general activities, while with the nurse the opposite state obtains. Certainly it is suggestive that these results may be due in part to secondary factors, whether the given individual is in a state of activity or rest. At least, in these experiments the parallelism between the degree of activity and the variation in the urinary findings seems most direct. The four patients were in bed throughout the entire period of observation, but were frequently restless and

<sup>5</sup> Although this last day at first suggests some loss of material I feel quite certain that all urine voided during the twenty-four hours is here represented. This experiment would no doubt have been of more complete value if continued for at least another day, but this could not be done.

uneasy, perhaps because previously they had been allowed to be up and about and could not accommodate themselves sufficiently well to the enforced rest necessitated by these studies. When the drug was in effect, even this restlessness was annihilated. On the other hand, the nurse was engaged with his routine duties up to the moment the hyoscine was given, and the added abnormal activity which this occasioned persisted for several hours. It has been shown,<sup>6</sup> however, that when the diet contains a sufficient amount of carbohydrates and fat the protein metabolism is not appreciably altered by muscular activities. The diet used here conforms to these requirements and, therefore, it is necessary to throw aside this factor as a possible explanation of the variations in the protein metabolism as found in these observations.

Whatever may be the cause or the specific manner in which the variations in the urinary constituents were produced, there has been apparently some interference through the action of these drugs with one or more steps at some point in the process of metabolism which has led to a general deviation from the normal in the amounts of the various urinary bodies as determined in these analyses. And the very fact that this deviation, whether an increase or the reverse, has been such that the usual ratios have not been changed, would seem to indicate that the force in effect has been of such a nature and has been applied at such a point as to occasion a retardation (or acceleration) of the metabolic processes at a stage at which all elements would be influenced equally. Looking at the question from this point of view, the following possibilities need to be considered:

1 There may have been some delay in the processes of absorption from the alimentary tract.

2 There may have been a variation in the intensity of tissue metabolism.

3 An interference with the elimination of normally formed products may have occurred.

That there may have occurred some delay in the absorption seems possible. The effect of morphine alone on the intestinal movements has been known for some time, but the work of Magnus has added much to this knowledge. Magnus<sup>7</sup> has shown that morphine causes a very high grade of retardation in the passage of food along the alimentary canal and that after the administration of morphine food remains in the stomach.

6 Wait Experiments on the Effect of Muscular Work on the Digestibility of Food and the Metabolism of Nitrogen, U S Dept of Agric, O E S Bull 117, 1902, p 40.

7 Magnus, R Die stopfende Wirkung des Morphins, Arch f d ges Physiol, 1908, cxxxii 210.

many hours longer than is normal. Such a stasis of the food would lead to a delay in absorption which would very probably cause a decrease in the amount of food metabolized, and this in turn would show itself in a decrease in the output of metabolic products during the period over which the drug was in action. And yet the reduction on the days when the drugs were given is not so very extensive—not so much as one might expect from the enormous delay that Magnus has shown to occur as the result of morphin alone. This suggests that the scopolamin may exert some antagonistic action, so that the full effect of the morphin is not brought into action. The effect of the scopolamin alone on the nurse might offer additional weight tending to corroborate this suggestion. Whether or not it would be justifiable to accept this, it seems that without doubt the effect of morphin in producing delayed absorption from the alimentary tract is one of the most important and prominent factors in explaining the deviation of metabolism as found in this study.

A decrease in the tissue metabolism is the second stage at which a general action of the drugs might be looked for. It would not be expected that a variation that would affect the metabolism of nitrogen would occur at this point, and, although such may be the case, there is no tangible evidence to support the conclusion that any of the metabolic processes were here interfered with so as to cause such variations in the urinary output as have been found.

The action of morphin on the intestinal movements would perhaps be of considerably more importance in considering the elimination of normally formed metabolic products through the feces. The slowing of bowel evacuations due to morphin was not particularly well marked in these cases. Unfortunately, as the feces were not divided into twenty-four-hour periods corresponding to the times when the urine was collected, the determination of the average daily output of the fecal constituents for the whole period of the experiment would offer no data of value in this connection. On this account these figures are not given here. The action of the members of the atropin group on the secretions in general might lead to the idea that it had exerted some effect on the renal secretion in the case of the patients. Besides the fact that the atropin is not supposed to exert directly much effect on the kidneys, however, we have the diametrically opposite effect produced in the nurse to whom the seopolamin was given alone. It is notable, too, that with the nurse the water content of the urine was but very slightly increased, so that the enormous relative increase in the amounts of the other constituents cannot be due to a flushing-out action of a sudden, large increase in the amount of the urine voided. That the entire variation may not be

imputed to an incompletely emptied bladder, it might be stated here that with all of the patients it was deemed advisable to use the catheter frequently in order to avoid, as far as possible, errors from this source. The third patient (E J D), for instance, in whom the decrease is exceedingly clearly shown on the second day, was catheterized both during the twenty-four hours and each day exactly at the time of ending of the period.

In the patients the decrease noticed was not merely a return to normal from a level already heightened by some unknown process incident to the diseased state. That this is true is seen in the fact that the amounts of the various urinary constituents excreted before the drugs were given is in most instances already decidedly lower than that which is considered the "normal" for this particular diet. With the nurse the amounts were definitely higher than this normal for the twenty-four hours during which the drug was administered.

#### CONCLUSIONS

Although generalizations cannot be drawn with final security from so limited a series of observations, it seems that the points brought out by these observations justify the following conclusions:

1 Scopolamin-morphin when given together in sufficient quantity and when leading to a depression of activities cause a decrease in the absolute amounts of nearly all of the normal constituents of the urine.

2 Scopolamin alone, when it leads to an elevation of activities, causes an increase of such constituents.

3 The increase or decrease affects all constituents about equally.

4 The effect of both drugs together or of the scopolamin alone is shown transiently not more than twelve hours and perhaps less, and on the day following the administration of the drugs the variation is partly counterbalanced by an increase or decrease, as the case may be.

5 Repeated doses of both drugs together over a long period of time will lead to a form of tolerance.

6 The influence on metabolism, as indicated by the variations in the urinary secretion, seems due to an indirect and secondary action of the drugs. The retardation of absorption from the alimentary tract is considered the prime cause for the variations found in the urine during these studies.

# PHYSIOLOGICAL AND PATHOLOGICAL EFFECTS OF SEVERE EXERTION (THE MARATHON RACE) ON THE CIRCULATORY AND RENAL SYSTEMS

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## INTRODUCTION

One of the decisive battles of the world was fought in year 490 B.C. Miltiades, a Greek general, commanding an army of but 11,000 men, defeated the Persians, numbering over 100,000. The conflict took place on the Marathon plain. After the battle a soldier was dispatched to carry the news of victory to Athens, a distance of 40 kilometers (24.85 miles). As he reached his destination, having run without stopping, and as he emitted the words, "Victory is ours," he fell dead.

In 1896 the Greek government established the course covered by this unknown soldier as an official event of the Olympic games. America was not especially interested in this until an American youth, in 1908, won the race. Since then it has become popular on this continent, it has, in fact, become almost a craze with the American boys to train for and compete in these races.

It can easily be seen what a fertile soil for study of the circulatory system such youths might furnish, and this study has, along certain lines, been made with fruitful results.

## HISTORICAL

In 1899 Drs. Williams and Arnold<sup>1</sup> studied a series of these cases. From 1900 to 1903 Drs. J. B. Blake and R. C. Larrabee<sup>2</sup> studied the contestants who ran in the Boston Athletic Association race. Since then a series of these have been studied by Drs. Nathaniel B. Potter and James T. Harrington<sup>3</sup>. The work reported so far is admirable and full of interesting findings, much of which all investigators in the future will find themselves repeating. The most difficult problem that presents itself to

\* Presented by invitation before the American Physiological Society, Dec. 30, 1909, Boston.

<sup>1</sup> Williams and Arnold. Effect of Violent and Prolonged Muscular Exercise on the Heart, Philadelphia Med. Jour., 1899, III, 1233.

<sup>2</sup> Blake, J. B., and Larrabee, R. C. Observations upon Long-Distance Runners, Boston Med. and Surgical Jour., 1903, CLVIII, 195.

<sup>3</sup> Potter, N. B., and Harrington, J. T. Medical Supervision of Athletics Among Boys at Boarding Schools, Jour. Am. Med. Assn. 1909, III, 1957.

the investigator along this line is the handling of these youths and men. In our work this was made comparatively easy for us by the Pittsburgh Athletic Association. They made it imperative that the contestants present themselves for examinations at the specified times, and with that they liberally furnished us everything necessary and convenient to make these studies successful in every possible way. For all this we wish to express our sincerest appreciation, and we feel that the results that they have made possible have warranted their liberality.

The work here considered is but one phase of the studies carried out by Dr Watson L. Savage, Dr John W. Boyce and myself. My part of the work is limited to the circulatory and renal systems, and I present the observations here in the order in which they were made.

The 55 contestants in this race were youths and men from the ordinary walks of life, and most of them were new recruits to this form of exertion.

#### PULSE-RATE DURING TRAINING

At some time during the week before the run we had the contestants count their pulse in the morning before getting out of bed and in the evening before retiring. They all ran their training distance on that day, which varied from 2 to 18 miles, the average being 7.

Table 1 shows the morning pulse to have been below 71 in 13 out of 16 cases, and the evening pulse was below 71 in 10 out of 16 cases. Taken as a whole, the pulse-rate is a little slower than what is considered normal for the average individual.

TABLE 1—MORNING AND EVENING PULSE DURING TRAINING

Morning Pulse			Evening Pulse		
	Cases			Cases	
40-50	1		40-50	0	
50-60	6		50-60	2	
60-70	6		60-70	8	
70-80	3		70-80	6	
	<hr/>	16		<hr/>	16

#### RELATION OF MORNING AND EVENING PULSE

I noticed that in about half of the number there was a marked difference between the morning and evening pulse-rate. In Table 2 these cases are separated in two groups. A further study brought out the interesting fact that those subjects who showed the greater diurnal variation had higher blood-pressure. And there was but one subject that showed high blood-pressure who did not have this marked diurnal variation.

The subjects in the second group are further advanced in life than those of the first group and a higher blood-pressure is to be expected, nevertheless, as will be seen later, these readings are higher than they should be, all things considered.

TABLE 2—MORNING AND EVENING PULSE DURING TRAINING

Age	Normal Variation			Age	Hypernormal Variation		
	A.M.	P.M.	B.-P.		A.M.	P.M.	B.-P.
18	72	68	110	20	52	53	140*
19	58	58	118	21	60	74	135
19	54	64	120	25	50	70	150
22	60	65	125	29	60	74	162
22	70	74	125	31	48	67	138
29	64	66	115	36	55	65	132
29	60	62	122	36	70	78	140
29	65	71	120	52	56	68	134

\* Exceptional case

## PULSE-RATE BEFORE THE RACE

The pulse-rate was taken in the horizontal position in all cases before the race. Half of them on the preceding evening and the others in the forenoon within three hours before the race. So far as could be estimated, the psychic influence of our investigations on these contestants at this time was not a considerable factor, as we made an effort to put them at ease so as to eliminate, if possible, such influence on the pulse-rate and blood-pressure readings.

Table 3 shows that, while the pulse varied from 50 to 110, in most cases it was normal.

TABLE 3—PULSE-RATE BEFORE RACE

No Cases	Pulse Rate	No Cases	Pulse Rate
2	50 55	10	80- 85†
0	55 60*	1	85 90
7	60 65*	2	90- 95
11	65 70*	2	95 100
9	70 75*	1	100 105
8	75 80†	2	105 110

Total number of cases, 55

\* Pulse rate 55 to 75, 27 cases † Pulse-rate 75 to 85, 18 cases

## BLOOD-PRESSURE STUDIES

These records were made with the Erlanger and the Stanton sphygmomanometers. They were both fitted with the same width rubber cuff (10 cm) and had been previously tested and compared. All the work referred to in this paper was performed with the instruments used in these observations.

Before the race we obtained complete records made with the Erlanger instrument in 24 cases and with the Stanton in 21. No attempt was made at reading the diastolic pressure with the Stanton instrument.

## NORMAL BLOOD-PRESSURE

As a basis for comparison in this series a curve was constructed based on 90 blood-pressure observations in normal males at the succeeding years. This is shown in Chart 1 and the succeeding charts of averages. Of the individuals of 60 and over, while it may be said that they should not be considered normal on account of the changes that are invariably present at that age, yet I can affirm that they were distinctly free from marked evidences of disease.

It will be noted that with the advance of years the curve gradually tends upward. This seems in accordance with the fact that the heart enlarges as the age of the individual progresses.

With this line as a normal level of the maximum blood-pressure, in all of my observations in the past, I have found that a variation of more than 25 mm above or below is usually associated with evidence of disease.

## MAXIMUM BLOOD-PRESSURE BEFORE RACE

These determinations were made with the Erlanger instrument eighteen hours before the race in 24 cases, and with the Stanton two hours before the race in the other 29 of the series. The average maximum blood-pressure of the entire series of 53 cases was 126.5 mm.

The average maximum of these cases, arranged according to the age, is shown in Table 4, which shows the constancy and regularity with which the blood-pressure rises as age advances.

TABLE 4.—AVERAGE MAXIMUM BLOOD PRESSURE BEFORE RACE IN 45 CASES

No.	Cases	Age	Average Maximum B.-P.
12		18-20	122.75
20		20-25	125.05
11		25-30	129.00
2		30-35	136.00

The average maximum, minimum and pulse-pressures of these contestants, first in the horizontal and then in the erect position of the body, is to be seen in Table 5. These cases are arranged in the order in which the contestants finished in the race. As is well known, the change of the body posture causes certain alterations in the relation of the pulse and blood-pressures. These are noted in the last column of the table as plus, minus and equal. The conclusions from these will be commented on later.

TABLE 5.—BLOOD PRESSURES BEFORE THE RACE IN HORIZONTAL AND ERECT POSTURES

No.	Age	Pulse	Horizontal				Erect				Result				
			B-P		B-P		B-P		B-P		P	S	D	P-P	
4	18	72	110	90	20	72	115	80	35	=	+	-	-	+	
5	28	105	132	98	34	97	128	95	33	-	-	-	-	-	
7	36	63	132	100	32	76	132	100	32	+	=	=	=	=	
11	19	78	120	85	35	90	120	80	40	+	=	-	-	+	
12	21	76	145	100	45	80	145	100	45	+	=	=	=	=	
13	22	74	125	100	25	76	122	100	22	+	-	=	-	-	
15	19	84	110	90	20	84	118	85	33	=	+	-	-	+	
17	23	106	135	90	45	106	135	100	35	=	=	=	+	-	
19	27	66	122	90	32	76	118	90	28	+	-	=	-	-	
22	21	80	130	100	30	83	132	110	22	+	+	+	-	-	
24	27	67	120	95	25	72	130	100	30	+	+	+	+	+	
27	19	54	118	92	26	74	112	92	20	+	-	=	-	-	
30	25	65	110	90	20	70	112	98	14	+	+	+	-	-	
32	52	82	134	100	34	78	138	100	38	-	+	=	=	+	
38	21	69	124	95	29	76	120	100	20	+	-	+	-	-	
39	19	87	155	130	25	84	142	118	24	-	-	-	-	-	
40	23	66	133	110	23	66	135	100	35	=	+	-	-	+	
41	?	64	130	92	38	64	132	90	42	=	+	-	-	+	
43	20	75	120	88	32	76	100	80	20	+	-	-	-	-	
47	29	83	162	112	50	85	150	105	45	+	-	-	-	-	
48	27	62	130	100	30	72	120	100	20	+	-	=	-	-	
49	27	72	130	95	35	70	132	100	32	-	+	+	-	-	
50	21	70	105	85	20	70	110	85	25	=	+	=	=	+	
51	18	76	118	95	23	83	110	95	15	+	-	=	-	-	
												+14	+10	+8	+8
												-4	-11	-9	-14
Average		74.8	127.8	96.7	30.3	78.3	124.9	95.9	29.3	=6	=3	=9	=2		

TABLE 6—MAXIMUM, MINIMUM AND PULSE-PRESSURE BEFORE RACE  
ACCORDING TO AGE

HORIZONTAL											
—Age 18 to 20—			—Age 20 to 25—			—Age 25 to 30—			—Age 35 to 40—		
Max	Min	P-P	Max	Min	P-P	Max	Min	P-P	Max	Min	P-P
110	90	20	145	100	45	132	98	34	132	100	32
120	85	35	125	100	25	122	90	32			
110	90	20	135	90	45	120	95	25			
118	92	26	130	100	30	110	90	20			
155	130	25	124	95	29	162	112	50			
118	95	23	133	110	23	130	100	30			
			120	88	32	130	95	35	AGE 52		
			105	85	20				134	100	34
Average											
121.8	97	24.8	123.3	96	31	129	98	32			
ERECT											
115	80	35	145	100	45	128	95	33	132	100	32
120	80	40	122	100	22	118	90	28			
118	85	33	135	100	35	130	100	30			
112	92	20	132	100	22	112	98	14			
			120	100	20	150	105	45			
142	118	24				120	100	20			
			135	100	35						
110	95	15				132	100	32	AGE 52		
			100	80	20				138	100	38
			110	85	25						
Average											
119.5	91.6	27.8	124.8	95.6	28	127	98.2	28.8			

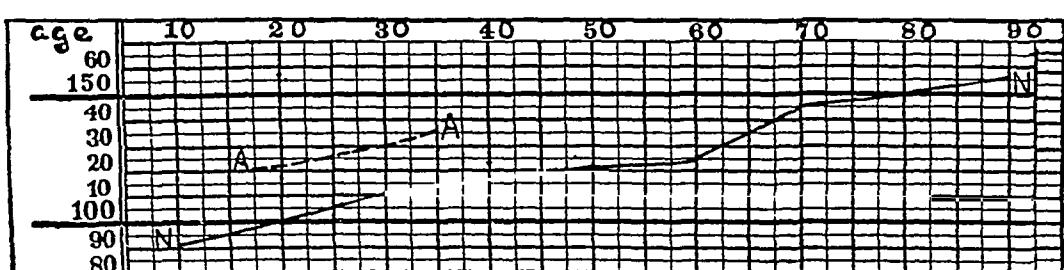


Fig. 1.—Average maximum blood-pressure (before the race) of contestants (line AA) compared with average maximum blood pressure in 90 normal men (line NN).

On the maximum blood-pressures in all the subjects at their respective ages I have constructed the chart shown in Figure 1 and it is to be noted that this curve is at about the upper limit of the normal blood-pressure zone.

## RELATION OF BODY WEIGHT TO BLOOD-PRESSURE

Table 7 shows that half of the overweighted subjects and a little over a third of the underweighted subjects had higher than average blood-pressure. Between the degree of overweight and the height of the blood-pressure there was no relation whatever.

TABLE 7—RELATION OF BODY WEIGHT TO BLOOD PRESSURE

53 Cases

	Cases	Hypertension
Underweight	34	10
Overweight	16	8
Normal	3	0

## RELATION OF OCCUPATION TO BLOOD-PRESSURE

The occupations were subdivided according to the amount of physical strain. Only those were classified with the hypertension cases whose pressures were distinctly above the average for the age of the subjects.

TABLE 8—RELATION OF OCCUPATION TO BLOOD PRESSURE

B-P Average	B-P Above Average
Professional	2
Clerk	7
Light Labor	6
Total	15
Heavy Labor	9

## RELATION OF PREVIOUS MARATHON RUNS TO BLOOD-PRESSURE

Some of the contestants were experienced long-distance runners, but most of them had partaken in long-distance races not more than one year, so that the extra strain thrown on the circulatory system was rather sudden and in some instances it was persistent during the entire year or less.

Table 9 shows the number of races run and the time of long-distance running. The runners showing high blood-pressure are in those who had trained for and run from three to five races within the first year of their experience. The experienced runners of nine, ten, eleven and twenty years all had average blood-pressure.

TABLE 9—PREVIOUS RUNS AND BLOOD-PRESSURE

Years	Long Dis Run	Marathon Races	Blood-Pressure
20		8	Average
11		3	Average
10		3	Average
9		4	Average
2		5	Average
1		5	High
1		5	High
1		4	High
1		4	Average
1		3	High
1		3	High
1		3	Average
1		3	Average
1		3	Average
1		2	Average

## HEART CASES

Auscultation was carried out in every one of the 55 contestants, within twenty-four hours before the race, with abnormal findings in seven cases, as shown in Table 10

TABLE 10—HEART CASES

	Cases
Systolic murmur at apex	4
Systolic murmur at pulmonic area	1
Muffled first sound at apex	1
Arrhythmia	1

On inspection, a considerable number showed very prominent apex beat, and in nearly all cases the impulse was plainly visible. Percussion was not carried out, as the presence of hypertrophy was to be determined by a more accurate method.

## BLOOD-PRESSURE IN HEART-MURMUR CASES

In each of the five murmur cases there was a maximum and minimum pressure distinctly above the normal line, and four of them showed a pressure very much higher than the average height.

Table 11 gives the readings in these cases, and Figure 2 shows their maximum blood-pressure as compared with the other athletes and normal individuals.

TABLE 11.—HEART-MURMUR CASES

Age	Max Blood-Pressure	Min Blood-Pressure
18	110	90
19	155	130
21	140	100
29	162	112
36	132	110

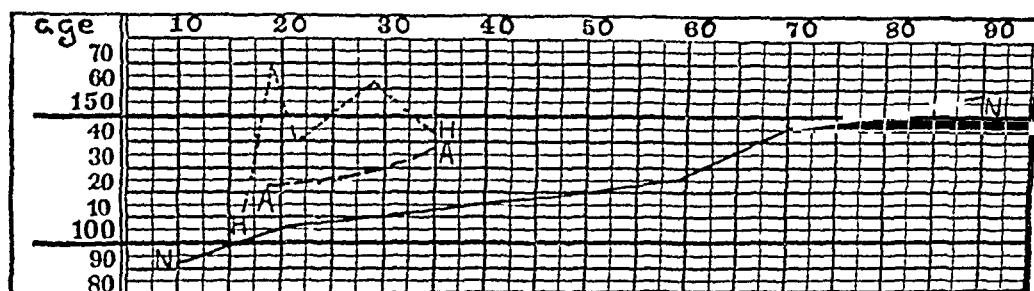


Fig. 2.—Average maximum blood pressure (line H-H) of five contestants with heart murmurs (before the race) compared with average maximum blood pressure of other contestants (line A-A) and of normal men (line N-N)

#### RELATION OF HEART CASES TO BODY WEIGHT

Having learned that in these cases there was no history of cardiac involvement from disease, I thought it might be of interest to search for other causative factors. We have studied the age, height and weight of these contestants and classified them as over, under and normal weight. The relation of these heart cases to the body weight is shown in Table 12.

TABLE 12.—BODY WEIGHT IN HEART CASES

Before Race		After Race	
Heart	Weight *	Heart	Weight
Intermittent	—	Intermittent	—
Syst Apex	N	Syst Base	—
Syst Apex	—	Syst Apex	N
Syst Apex	—	Syst Apex	—
Syst Apex	+	Irreg	—
Syst Pulmonic	+		
Airhythmia	—		

\* In this column + means overweight, —, underweight, and N, normal

The table shows that the murmurs were entirely independent of body overweight, and that the proportion of underweight cases is about the same as in the entire series.

## BLOOD-PRESSURE AFTER THE RACE

The blood-pressure readings were made immediately after the finish in nearly every case. In only a few instances was it delayed four or five minutes after entrance to the medical tent. For comparison, the readings obtained before the race are repeated in the following tables. The average of the maximum pressures before the race was 126.5 (53 cases) and 107.3 (38 cases) after the race.

Table 13 gives the readings in the individual cases after the race and the average pulse-rate, maximum, minimum and pulse-pressures, in the horizontal and erect postures. The effects resulting from the change of posture are to be noted in the last column.

TABLE 13.—PULSE-RATE AND BLOOD-PRESSURE IN HORIZONTAL AND ERECT POSTURES AFTER THE RACE

No.	Age	Pulse	Horizontal			Erect			Result						
			B	P	S	D	P-P	Pulse	S	D	P-P	P	S	D	P-P
4	18	93	95	88	7	112	98	90	8	+	+	+	+	+	+
5	28	120	95	80	15	138	90	?	?	+	—				
7	36	112	88	?		120	88	?		+	=				
11	19	112	100	70	30	112	108	75	33	=	+	+	+	+	+
12	21	100	108	80	28	108	100	80	20	+	—	=	—	—	—
13	22	96	94	74	20	100	92	80	12	+	—	+	—	—	—
15*	18	104	105	80	25	120	110	75	35	+	+	—	—	—	+
17	23	106	100	80	20	116	88	75	13	+	—	—	—	—	—
19	27	93	110	85	25	114	100	85	15	+	—	=	—	—	—
22	21	90	100	82	18	96	85	70	15	+	—	—	—	—	—
24	27	80	110	72	38	93	105	80	25	+	—	+	—	—	—
27	19	80	114	90	24	116	108	90	18	+	—	=	—	—	—
30	25	81	110	95	15	96	110	92	18	+	=	—	—	+	—
32	52	106	118	92	26	129	108	90	18	+	—	—	—	—	—
38	21	81	80	75	5	99	95	80	15	+	+	+	+	+	+
39	19	108	92	78	14	120	82	72	10	+	—	—	—	—	—
40	23	114	108	88	20	135	108	88	20	+	=	=	=	=	=
41	?	60	122	88	34	81	130	100	30	+	+	+	—	—	—
43	20	92	120	88	32	110	100	80	20	+	—	—	—	—	—
												+19	+5	+6	+5
												=1	-12	-8	-12
Average			95.6	103.6	82.5	22	111.3	100.2	82.4	19.1	—3	=3	=4	=1	

The averages of the readings after the race (Table 13), as compared with the findings previous to the race, are shown in Table 14.

TABLE 14.—PULSE-RATE, MAXIMUM, MINIMUM AND PULSE PRESSURE, BEFORE AND AFTER THE RACE

	Cases	Horizontal				Erect			
		Pulse	Max	Min	P-P	Pulse	Max	Min	P-P
Before	21	74.8	127.8	96.7	30.3	78.3	124.0	95.9	29.3
After	19	95.6	103.6	82.5	22.0	111.3	100.2	82.4	19.1

Arranged according to age, the individual readings are to be seen in Table 15.

TABLE 15.—MAXIMUM, MINIMUM AND PULSE-PRESSURE AFTER RACE, ACCORDING TO AGE OF SUBJECTS

HORIZONTAL											
—Age 18 to 20—			—Age 20 to 25—			—Age 25 to 30—			—Age 35 to 40—		
Max	Min	P-P	Max	Min	P-P	Max	Min	P-P	Max	Min	P-P
95	88	7	108	80	28	95	80	15	88	?	?
100	70	30	94	74	20	110	85	25			
105	80	25	100	80	20	110	72	38			
114	90	24	100	82	18	110	95	15			
			80	75	5						
92	78	14									
			108	88	20						
			120	88	32				118	92	26
<i>Average</i>											
101.2	81.2	20	101.4	81	20.4	106.2	83	23.2			
ERECT											
98	90	8	100	80	20	90	?	?	88	?	?
108	75	33	92	80	12	100	85	15			
110	75	35									
			85	70	15	110	92	18			
108	90	18									
			95	80	15						
82	70	10									
			108	88	20						
			100	80	20				108	90	-18
<i>Average</i>											
101.2	80.4	20.8	95.4	79	16.4	101.1	85.6	19.3			

The chart shown in Figure 3 is based on the readings obtained immediately after the race. It shows the normal curve, the curve based on the average of all the cases after the race, and the blood-pressure readings in

the muimui cases. It will be noted that the total average curve is now below the normal line, whereas before the race it was about 25 mm above the line. It will also be noted that the muimui cases suffered a greater fall than the others.

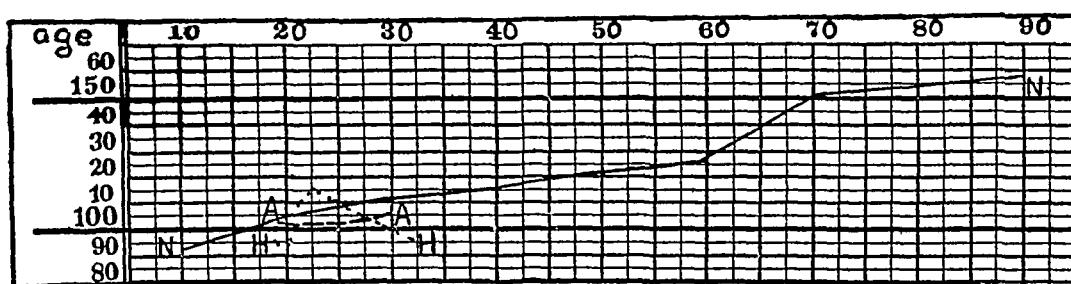


Fig. 3.—Average maximum blood-pressure after the race in the contestants with heart muimuis (line H-H) and in all contestants (line A-A) compared with normal curve (line N-N).

#### HEART CASES IN THE RACE

Of the 5 runners who had murmurs before the race, 4 ran the full distance and one ran nineteen miles. Three of these were among the first 12 to finish the race. These runners were all new to long-distance running.

After the race the hearts were auscultated in the first 45 as they finished. Out of the 29 that finished within the time limit (four hours, fifteen minutes) 5 presented heart conditions. Table 16 shows the place in which they finished. The fourth column in Table 16 shows the proportion of the pulse-pressure after the race to that before.

TABLE 16.—PULSE-PRESSURE BEFORE AND AFTER THE RACE IN RUNNERS WITH HEART SYMPTOMS

Finished	Before Race	After Race	Pulse-Pressure After	Pulse-Pressure Before
2nd	Muffled apex first	Intermittent and weak		
3rd	O	Systolic base		
4th	Systolic apex	Systolic apex	7	20
5th	O	Systolic apex	15	34
7th	Systolic apex	O	?	32
12th	Systolic pulmonic	O	20	45
29th	O	Irregular		
39th	Systolic apex	O	10	29
47th	Systolic apex	Not examined		
50th	Arrhythmia	Not examined		

These "heart subjects" had more rapid pulses and smaller pulse-pressures as a result of the exertion. Their blood-pressures are shown in the charts, Figures 2 and 3.

#### BLOOD-PRESSURE TEN DAYS SUBSEQUENT TO THE RACE

At this time we find the blood-pressure about the same as before the race, or, rather, it was nearer the normal line than before.

TABLE 17—AVERAGE MAXIMUM BLOOD-PRESSURE BEFORE, IMMEDIATELY AFTER, AND TEN DAYS SUBSEQUENT TO THE RACE

	Cases
Before	126.5
Immediately after	107.3
Ten days subsequent	124.7

Table 18 shows the average pulse-rate, maximum and minimum, and pulse-pressures in the horizontal and erect postures, as compared with the tables of the same data before and after.

TABLE 18—AVERAGE MAXIMUM, MINIMUM AND PULSE-PRESSES TEN DAYS SUBSEQUENT TO RACE

	No	Cases	Horizontal				Erect			
			Pulse	Max	Min	P-P	Pulse	Max	Min	P-P
Before		24	74.8	127.8	96.7	30.3	78.3	124.0	95.9	29.3
Immediately after		19	95.6	103.6	82.5	22.0	111.3	100.2	82.4	19.1
Ten days subsequent		17	61.8	124.7	92.1	33.7	68.2	125.1	93.2	31.2

The readings in the individual cases are to be seen in Table 19, and these cases, arranged according to age of subjects, are given in Table 20.

TABLE 19—INDIVIDUAL MAXIMUM, MINIMUM AND PULSE-PRESSES TEN DAYS SUBSEQUENT TO RACE

No	Age	Pulse	SUBSEQUENT														
			Horizontal						Erect						Result		
			B-P			B-P			B-P			B-P			S	D	P-P
4	18	50	125	88	37	52	130	95	35	+	+	+	+	+	-	-	-
5	28	76	119	90	29	80	120	90	30	+	+	+	=	=	+	+	+
7	36	64	124	87	37	70	118	100	18	+	-	+	+	+	-	-	-
11	19	62	120	85	35	80	130	100	30	+	+	+	+	+	-	-	-
12	21	68	152	100	52	74	152	100	52	+	=	=	=	=	+	+	+
13	22	63	110	75	35	66	110	80	30	+	=	+	+	+	-	-	-

TABLE 19—CONTINUED

SUBSEQUENT														
Horizontal						Erect						Result		
						B-P								
15	18	52	120	95	25	70	122	92	30	+	+	—	+	—
17	23	73	118	80	38	90	120	90	30	+	+	+	—	—
19	27	48	130	100	30	52	138	98	40	+	+	—	+	+
22	21	72	138	90	48	90	128	98	30	+	—	+	—	—
24	27	78	120	90	30	76	120	90	30	=	=	=	=	=
27	19	66	135	88	47	54	120	92	28	—	—	+	—	—
30	25	56	112	92	20	58	112	92	20	+	=	=	=	=
32	52	56	144	110	34	64	155	110	45	+	+	=	+	+
38	21	56	110	88	22	52	110	78	32	—	=	—	+	+
40	23	62	125	100	25	66	132	100	32	+	+	=	=	+
43	20	56	118	88	30	66	110	90	20	+	—	+	—	—
—	—	—	—	—	—	—	—	—	—	+14	+8	+8	+6	
										—2	—4	—3	—8	
Average	61.8	124.7	92.1	33.7	68.2	125.1	93.2	31.2	=1	=5	=6	=3		

TABLE 20—PRESSURE READINGS TEN DAYS SUBSEQUENT TO RACE,  
ARRANGED ACCORDING TO AGE OF SUBJECTS

HORIZONTAL											
Age 18 to 20			Age 20 to 25			Age 25 to 30			Age 35 to 40		
Max	Min	P-P	Max	Min	P-P	Max	Min	P-P	Max	Min	P-P
125	88	37	152	100	52	119	90	29	124	87	37
120	85	35	110	75	35	130	100	30			
100	95	25	118	80	38	120	90	30			
135	88	47	138	90	48	112	92	20			
			110	88	22						
			125	100	25						
			118	88	30						
AGE 52											
Average											
120	89	36	124.3	90	35	120	70	27			
ERECT											
130	95	35	152	100	52	120	90	30	118	100	18
130	100	30	110	80	30	138	98	40			
122	92	30	120	90	128	120	90	30			
120	92	28	128	98	30	112	92	20			
			110	78	32						
			132	100	32						
			110	90	20						
AGE 52											
Average											
125	72	30	123	90.8	46	122	92	30	155	110	45

Six months later we examined five of these runners and found the blood-pressure lower than at the previous examination, their pressures were gradually lowering toward the normal average. The readings in these cases are seen in Table 21.

TABLE 21.—PRESSURE READINGS IN FIVE CASES SIX MONTHS AFTER RACE

HORIZONTAL									
Age 18 to 20			Age 20 to 25			Age 25 to 30			
Max	Min	P-P	Max	Min	P-P	Max	Min	P-P	
120	90	30	122	98	24	110	84	26	
120	86	34							
106	84	22							
<i>Average</i>									
115	86	28	122	98	24	110	84	26	
VERTICAL									
110	86	24	130	100	30	110	82	28	
110	85	25							
112	90	22							
<i>Average</i>									
110	87	23	130	100	30	110	82	28	

The chart shown in Figure 4 is based on the findings at the examinations ten days and six months after the race. The curve at the final examination is nearer the normal level.

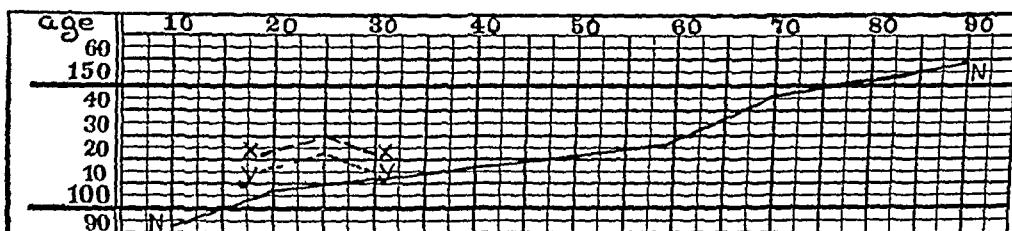


Fig. 4.—Average maximum blood-pressure (all contestants) obtained ten days (line X-X) and six months (line Y-Y) after the race, compared with normal curve (line N-N).

Each of the four charts 5, 6, 7 and 8 represents the blood-pressure curve of an individual case. They all show the marked fall resulting from the exertion, the height of the blood-pressure ten days after the race and the extent to which it had fallen at the end of six months. In the case of M—e it will be noted that at the end of six months his blood-pressure did not recede toward the normal level as the others, the reason for this is that he had kept up his training and long-distance running to the very day of the last examination. With the high pressure he

still had the mitral systolic loud blowing murmur which he presented at all of the previous examinations

In the last case, that of O—n, who had a murmur before and immediately after the race, it was found ten days later that the murmur could be brought out only by his pacing, and at the end of six months, even after pacing for a full half minute, it could not be heard. In this case, with the disappearance of the hypertrophy which was accompanied by a falling of the blood-pressure, there was a simultaneous disappearance of the murmur.

#### COMPARISON OF BLOOD-PRESSURE OBSERVATIONS BEFORE, IMMEDIATELY AFTER AND TEN DAYS AND SIX MONTHS SUBSEQUENT TO THE RACE

On the tables 1 to 21 I have constructed Charts 1 to 9. All considered, the conclusions from these evidences are that as a result of training for the Marathon race a state of increased blood-pressure is developed, which is considerably above normal. In some cases when training is

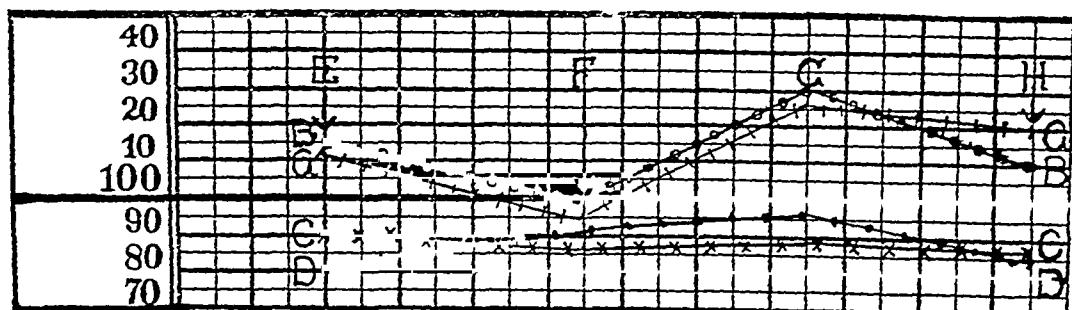


Fig 5.—Blood-pressure, case of H-n, line A-A, maximum horizontal, line B-B, maximum erect line C-C, minimum horizontal, line D-D minimum erect, E, before race, F, immediately after, G, ten days, and H six months subsequent to race

carried to a more severe degree or because of a preceding state of the heart we find still higher blood-pressure associated with heart murmurs.

As a result of the race the maximum, minimum and pulse-pressure in all cases are lowered, reaching a point below the normal average, and in the "heart" cases a greater fall is suffered than in the others.

Ten days subsequent to the race we find the blood-pressure about the same as before the race, or, rather, it is nearer the normal line. Six months after the race we find the blood-pressure lower than it was at the previous examination, i.e., still nearer to the normal.

#### EFFECT OF CHANGE OF POSTURE ON BLOOD-PRESSURE

The observations were made first in the horizontal and then in the erect posture. The surrounding conditions were as follows. Being in

June, the external temperature was warm. The contestants were stripped, they had been weighed, measured, hearts auscultated, all of which allowed them about ten minutes in the room previous to the blood-pressure examination. They then walked over to the table and lay down, after which the armlet was applied. Within three to five minutes the reading was

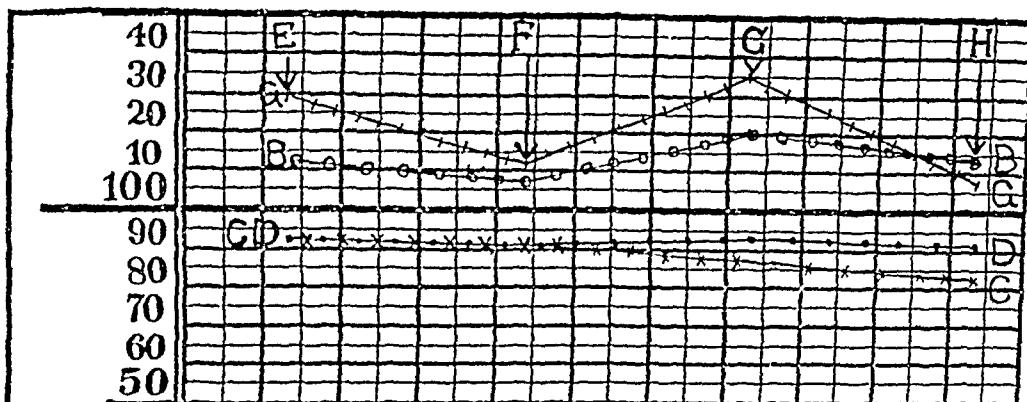


Fig 6.—Blood-pressures, case of Me, maximum and minimum, horizontal and erect, and times of examination indicated as before. Mitral systolic murmur heard at each examination.

made. Without removing the cuff they were directed to get up and stand beside the table not being allowed to lean against it, while the second reading was made. After the race they were laid on the table imme-



Fig 7.—Blood pressures, case of H-s, maximum and minimum, horizontal and erect, and times of examination, indicated as before.

diately on entering the medical tent (on a run). While I was making the blood-pressure observation another man counted the pulse. When this was done, the contestant was directed to get up, in many instances having to be assisted, to stand as erect as possible without leaning against the table while the second reading was being made. The technic of the subsequent examinations was the same as that of the first. This change from

the horizontal to the erect posture caused alterations in the blood-pressure which may be seen in the last columns of Tables 5, 14 and 19. These effects are summarized in Table 22.

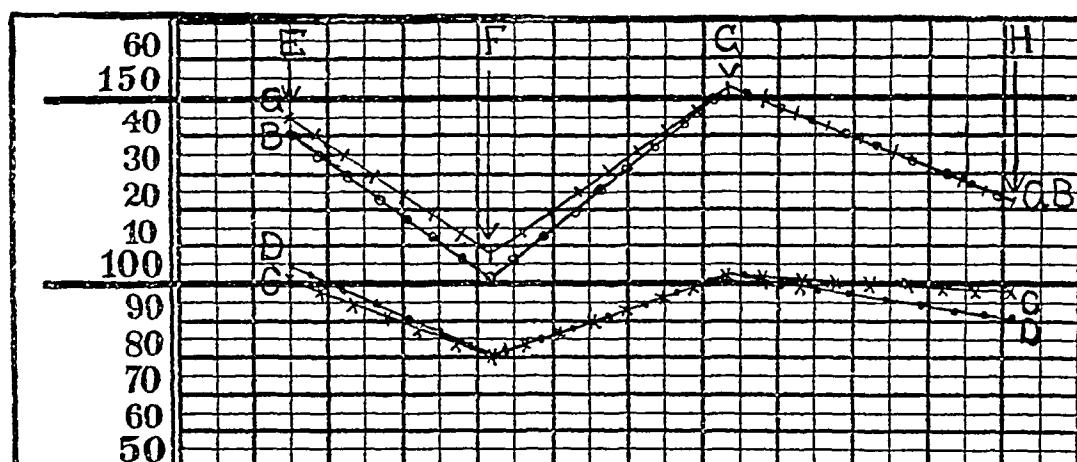


Fig. 8.—Blood pressures, case of O-n maximum and minimum, horizontal and erect, indicated as before Pulmonary systolic murmur heard before, after, and at the third examination, but at the time of the fourth examination it had disappeared.

TABLE 22.—EFFECT OF CHANGE OF POSTURE ON BLOOD-PRESSURE

	BEFORE RACE		
	Increased No Cases	Diminished No Cases	Unchanged No Cases
Pulse	14	4	6
Maximum	10	11	3
Minimum	6	9	9
Pulse-Pressure	8	14	2
	IMMEDIATELY AFTER RACE		
Pulse	19		1
Maximum	5	12	3
Minimum	6	8	4
Pulse-Pressure	5	12	1
	TEN DAYS SUBSEQUENT TO RACE		
Pulse	14	2	1
Maximum	8	4	5
Minimum	8	3	6
Pulse-Pressure	6	8	3

#### CONCLUSIONS IN REGARD TO EFFECT FROM CHANGES OF POSTURE

*Before Race*.—From these observations we may then say that in individuals with sound hearts having a definite degree of hypertrophy as a

result of change in posture, from the horizontal to the erect, there is a rise in pulse-rate, the maximum pressure may be increased or diminished, the minimum pressure may be diminished or equal, and with this there will be a diminution of pulse-pressure. This occurs in more than half of the cases.

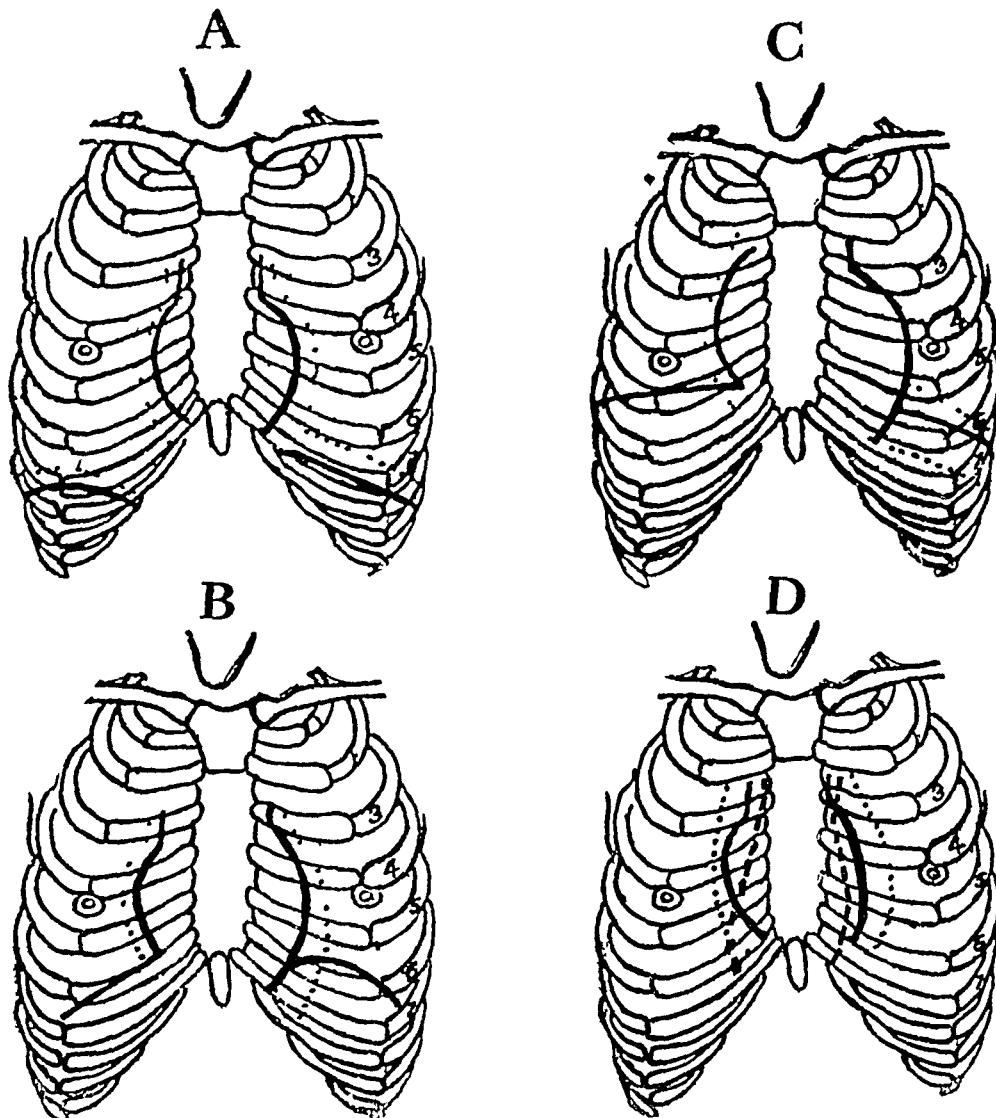


Fig 9.—Fluoroscopic studies made by Drs John W Boyce and George W Grie. Solid line indicates examination before, dotted line, immediately after, and line composed of dashes, examination a week after the race. A, small heart, contestant dropped out at one mile, B, heart right size, contestant finished No 11, C, large heart, left dilatation, D, average case.

*Immediately After Race*.—Following severe muscular exertion, in the greater number of cases, the change from the horizontal to the erect posture causes an increase in pulse-rate, a falling of maximum and minimum pressure, and with this a lowering of pulse-pressure.

*Ten Days and Six Months Subsequent to the Race*—The changes were the same as before the race

*Effect of Change of Posture in Heart Cases*—So far as could be seen these cases did not show a more striking uniformity in reaction to the change of posture than the other cases

*Relations of Maximum, Minimum and Pulse-Pressures to Each Other*—In most of these records it will be seen that the height of the minimum pressure was in proportion to the maximum, and that the pulse-pressure was greatest in those cases showing the highest maximum pressures

#### RELATION OF X-RAY FINDINGS TO BLOOD-PRESSURE

This work was carried out by Dr John W Boyce and Dr George Grier with their assistants at the West Penn Hospital. They classified the cases examined before the race as (a) small hearts, (b) hearts of the "right size" and (c) large hearts. Those of the first group were not small as compared to normal hearts, they were, in fact, larger than normal, but they were the small hearts of this series. The average maximum blood-pressure of the small heart cases was 124 mm, while the average of the hearts of the "right size" and large heart series was 138 mm. Of six cases that had "small hearts," none finished the race. Of 17 that had hearts of the "right size," seven finished. This means that with the compensatory hypertrophy there comes increased endurance. After the race, within three-quarters of an hour in most instances, tracings of heart shadows were again made. The degree of dilatation varied.

The average fall in the cases of maximum pressure as a result of the race in those cases presenting a large degree of dilatation, was 31 mm, while the average fall of maximum pressures in those outlined as showing little change in the heart shadow was 12 mm.

#### RENAL SYSTEM

*Before Race*—The urine was examined in 24 cases. One showed less than 0.1 per cent of albumin, which was not of renal origin. There were no casts in any. On standing over night, crystals of calcium oxalate were deposited in five specimens.

*Immediately After Race*—Amount We succeeded in getting 19 specimens, and in those the total quantity excreted during the time of the race, which lasted between three hours and fourteen minutes to five hours. The largest amount was 220 cc and the smallest was 35 cc.

Color This varied from normal to dark smoky amber, in several it was bloody.

**Reaction** This was alkaline in those containing considerable blood, and in the others it was acid.

**Specific Gravity** This varied from 1012 to 1035. There was no ratio between the amount and the specific gravity.

**Total Solids** These varied from 22 gm to 1351 gm. The presence of blood makes the estimation valueless. Even on eliminating the cases in which there was considerable blood in the urine, I could find no ratio between the solids and the loss of body weight during the race, nor to the total amount of urine.

**Albumin** Every specimen showed albumin from mere trace to a heavy cloud.

**Sugar** A positive reaction was not obtained in any case.

**Acetone Bodies** Diacetic Acid With ferric chlorid a typical reaction was obtained in 3 cases, it was distinctly present in 10, and in large amounts in 4 cases. It was absent in the case in which there was the largest amount of urine passed and present in small amount in the next largest specimen. Acetone The acetone reaction was less marked, but present. Beta-oxybutyric acid was tested and found in one of the specimens. The nature of the diacetic and acetone reactions was verified by H. L. Amos of the West Penn Hospital, to whom I am indebted for the examination of a number of specimens.

**Microscopic Examination** Every one of the 19 cases showed casts. Five of them showed "showers of casts." All but the largest specimen showed red blood cells, three showed large amounts of blood. In one specimen I found fat globules.

*At Subsequent Periods*—Out of the 19 specimens examined at the end of a week, 4 showed light clouds of albumin and as many had casts. Two showed casts without albumin.

Three weeks after the race, 3 that did not show albumin before the race still showed traces of albumin and casts.

TABLE 23.—URINARY FINDINGS BEFORE THE RACE, IMMEDIATELY AFTER AND AT SUBSEQUENT PERIODS

	No. of Cases	Albumin	Blood	Casts	Acet. Bodies
Before	24	1	0	0	0
Immediately after	19	19	18	19	18
One week subsequent	19	4	0	6	0
Three weeks subsequent		3	0	3	0

RELATION OF CIRCULATORY TO RENAL SYSTEM (AS ESTIMATED BY URINARY FINDINGS)

Table 24 gives the age, maximum and pulse-pressures before and after the race in the horizontal position, the amount of urine and approximate amounts of albumin and acetone bodies

TABLE 24—RELATION BETWEEN CIRCULATORY AND RENAL SYSTEM (URINARY FINDINGS)

Age	Hor Max	B -P Before P -P	Urine		Hor Max	B -P After P -P	Acet Bodies
			C C	Albumin			
18	140		220	I	100		
36	140		205	I	110		
25	145		200	½	130		
27	122	32	195	I	110	25	I
19	122		195	I	110		
18	122		190	III	96		
?	115		190	II	88		
?	120	32	175	I	120	32	II
31	138		170	II	92		
36	132	32	170	III	88	?	III
?	132	38	170	I	122	34	O
52	134	34	150	I	118	26	I
19	118	26	130	½	114	24	IV
25	110	20	125	I	110	15	I
20	115		120	I	98		
20	115		75	III	130		
21	135	45	35	III	108		
23	135	45	?	III	100	20	I

From this table it may be seen that the subjects having the highest maximum pressures before the race excreted the largest amounts of urine during the race. The pulse-pressures were obtained in only part of this series, and their relation to the amount of urine seems variable.

Albumin was present in small amounts in the cases in which the larger quantities after the race were passed.

Albumin was present in largest amounts in those cases which show the greatest fall in the maximum blood-pressures, and in those which showed the most marked falls in the pulse-pressures.

From these observations on the renal functions, it seems that the more serious the disturbance of the general circulatory system, the more marked are the evidences of this disturbance in the renal circulation, and

this is evidenced by the amount of blood, degree of albuminuria and cylindruria.

As to diacetic acid, all considered, it seems that it was found in larger amounts in the urine from those who ran most successfully—i.e., those who ran hardest in the shortest time. Undoubtedly, many other factors play a part in this. The amount of acetone seemed small in proportion to the diacetic acid, one way to account for this is perhaps that it was largely eliminated by the respiratory effort.

#### CONCLUSIONS

In the conclusion of this study, it may be said that the most marked changes which occur in the contestants who train for and compete in this race are as follows:

*Before the Race*—The average individual who has trained for this race will about the time he is in good training condition, have a pulse that is moderately slower than normal, with a normal diurnal variation. His blood-pressure is higher than that of the average individual, and with this he has developed a compensatory hypertrophy. If in his case it is found that he has a greater than normal diurnal pulse variation, that will be associated with a higher than average blood-pressure.

Or we may say that from these observations we are led to believe that the individual who has this more than average compensatory hypertrophy and higher blood-pressure, will have a greater number of heart-beats in the twenty-four hours. The average heart shadow as seen with the x-ray is larger than normal in nearly all cases, and some will show comparatively very large hearts. The subjects showing the largest hearts are the ones that have the higher blood-pressure.

In the contestant who as a result of hard training, or because of some unknown preceding state of his heart, has developed a heart murmur, there will be found the very large heart and higher blood-pressure. Body overweight, laborious occupation, short and severe training are productive of higher than average blood-pressure and associated hypertrophy.

*After the Race*—As a result of this inordinate exertion, if he is of the average class, he will have a fall of about 20 per cent in his blood-pressure, if he is of the "heart-murmur cases," he will have a still greater fall in his blood-pressure. If his heart shadow with the x-ray shows a marked increase in size (much dilatation), his blood-pressure will have a greater fall than if his heart shadow remains about the same size (slight dilatation).

At the end of six months the blood-pressure is still nearer the normal level than at the previous examination.

Most of these contestants had been running during the preceding six or nine months, and it is natural to expect a gradual disappearance of the established hypertrophy, as our findings bear out.

The change of posture from the horizontal to the erect is followed by certain accommodative changes in the blood-pressure, these depending largely on the reserve energy of the circulatory system, and the promptness with which it reacts to the force of gravity.

The effect of this severe bodily exertion on the kidneys is definitely proportionate to the degree of general circulatory disturbance, of which the renal circulation is part.

In these studies we have had the rare opportunity of observing the transition stage from health to disease. Beginning as physiologic changes many of these cases have transgressed the dividing zone entering into that of the pathological. The exciting factors once removed, a recession into the normal followed, in some cases reaching the physiological quickly, others slowly, while some, it may be, will never return to normal.

In closing, I wish to say that for the opportunity of studying these cases, and for innumerable suggestions that made this work possible, I am deeply indebted to Dr Watson L Savage, Physical Director of the Pittsburg Athletic Association, and Carnegie Technical Schools, and then to express my sincerest thanks to the men whose names are here appended, for their careful, valuable and enthusiastic assistance. Without their aid such an undertaking as this would have been impossible.

DR E S DICKEY,  
DR O B McAFOY,  
DR C ORBIN,  
DR C L PALMER,  
DR FRANK D STOLZENBACH,  
DR H G WERTHEIMER,  
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# PROTEIN METABOLISM IN PNEUMONIA

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It might be assumed in a disease of such common occurrence and such fundamental importance in medicine as pneumonia that a very complete account of the protein metabolism would be available, especially in view of the fact that the conditions of the disease are such as to put at the disposal of the observer a sudden change in the condition of the patient from a condition of high temperature, great dyspnea and rapid heart action, to a normal state, which scarcely has a parallel among other diseases Incident to this, one has also a rapid change in the anatomical condition of a vital organ, the lung, in which as Muller, and his pupil, Simon,<sup>1</sup> showed, large quantities of soluble and partially digested protein products are thrown into the circulation and are catabolized

## OBSERVATIONS OF EARLY INVESTIGATORS

In examining the literature bearing on the metabolism of the disease, one is struck with the relatively small amount of accurate information In some instances determinations of the daily output of nitrogen have been made, many without reference to the nitrogen of the food In most other instances investigators have contented themselves with an examination of a single component of the urine, such as uric acid, chlorides, xanthin bases, etc As a matter of fact, the work which was done forty years ago by Huppert and Riesell<sup>2</sup> is more instructive and gives a clearer picture of the effect of the infective process on the elimination of nitrogen than any of the late investigations Even before their time also there were observations which showed the excessive amount of nitrogen eliminated

## TOTAL NITROGEN

Parkes, in his excellent book on "The Composition of the Urine" (London, 1860), gives the amount of urea found by a number of observers, and adds the report of a case examined by himself in which 85.38 gm

\* From the Department of Chemistry, Cornell University Medical College, and the Fourth Medical Division, Bellevue Hospital

<sup>1</sup> Deutsch Arch f klin Med., 1901, lxx 604

<sup>2</sup> Huppert and Riesell Arch d Heilkunde, vii, 10, 1869, x, 329

of urea were eliminated in a single day. This amount of urea would be equivalent to 40.7 gm of nitrogen. As Parkes states that the patient was in a condition of fasting, this amount of nitrogen would be equal to 1,200 gm of muscle or other tissue of a similar composition furnished by the body to carry on the metabolism during the period of hyperpyrexia. That the infective process was greatly concerned in this elimination of nitrogen will readily be seen when it is noted that 40 gm of nitrogen is probably three times as much as a fasting subject would excrete under normal conditions of health.

Huppert and Riesell's observations were carried on with the elder Voit's investigations in mind. Not only was the nitrogen of the urine estimated, but also the nitrogen contained in the food, the sputum and the feces. In this way an accurate balance could be struck. The amount of nitrogen in the food during the period of hyperpyrexia and the resorption of the exudate was inconsiderable. The minus balance from day to day varied from 15 to 25 gm, the highest negative value being found on the day of beginning resorption. The following days, in which the patient took 4 gm of nitrogen, there was still a marked daily deficit. It was only on the sixth day after resorption had begun that the loss in nitrogen suddenly decreased, coincidently, however, with the administration of food containing 16.7 gm of nitrogen. A retention of nitrogen was arrived at on the twelfth day with 25 gm of nitrogen intake. Huppert and Riesell conclude that in conditions such as pneumonia the patient burns the cellular protein in contradistinction to the nutritive protein, which the healthy individual uses for catabolism. In this they approach very closely the idea of toxic destruction of protein so much debated by late writers.

In recent years the work of Moraczewski<sup>3</sup> on the metabolism in pneumonia appears to be more complete than that of any other observer. His studies of the protein metabolism in fever were directed to show that the tissues imbibed water during the course of hyperpyrexia and that this imbibition of water determined the increased protein decomposition. He attempted to ascertain if by "salting out" the blood it might be possible to inhibit increased destruction of protein. Moraczewski was one of the first to make an attempt to fractionate the components of the nitrogen elimination. Unfortunately, a close examination of the analytical results which this investigator furnishes does not lead one to place great weight on his work. His theoretical conclusions and his methods of experimentation (the administration of silver nitrate to reduce chlorid content of the

<sup>3</sup> Moraczewski Ztschr f klin Med 1900, xxix, 44, Virchow's Arch f path Anat, clv 11

blood) have been subject to what appears to be just criticism by Magnus-Levy.

Von Jaksch<sup>4</sup> has also made a comparative study of pneumonia and typhoid fever. He finds a notable difference in the manner in which the nitrogen compounds of the urine are eliminated in the two diseases.

According to this observer, pneumonia is classed with those diseases in which the nitrogen partition is normal, none of the nitrogen which is normally excreted as urea being used for the formation of other compounds. On the other hand, the catabolism in typhoid fever, according to von Jaksch, takes a distinctly abnormal course and instead of urea being eliminated in its normal ratio to total nitrogen the substance is replaced by other compounds—leucin, tyrosin and unknown substances. Unfortunately here also the methods employed for the analyses have been open to criticism, and von Jaksch has subsequently been forced to retract many of the statements which he previously made regarding the metabolism in these conditions. To what extent von Jaksch's statements regarding typhoid are corroborated may be seen from the work which has been done by Ewing and one of us<sup>5</sup> in a recent paper.

#### TOTAL SULPHUR

The total sulphur is taken up at this place before the distribution of the nitrogen is discussed, for the reason that the total sulphur in conjunction with the total nitrogen might give data regarding the type of protein metabolized at different stages of the disease.

As sulphur occurs in all protein with few exceptions, and as the sulphur content varies between 0.3 and 2.2 per cent, and the nitrogen content of protein varies between 15 and 17 per cent, there is a margin in the relation of sulphur to 100 parts of nitrogen of 1.7 to 14.6 per cent.

The relation of sulphur to nitrogen in normal urine is, however, a comparatively fixed value, being in the neighborhood of 7 per cent. With the ingestion of protein of varying sulphur content the organism apparently adapts the catabolism of the two compounds in such a way that the two are excreted in a fairly fixed ratio. It might be permissible to assume however, in pathological conditions, especially those associated with the breaking down of large quantities of body protein, that the ratio of nitrogen to sulphur in the urine might be disturbed, and so one might obtain information regarding the catabolism of some special type of protein.

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<sup>4</sup> Von Jaksch Ztschr f klin Med, 1902, xlvii, 1, 1903, L, 167

<sup>5</sup> Ewing, J., and Wolf, C G L. The Clinical Significance of the Urinary Nitrogen III Nitrogenous Metabolism in Typhoid Fever THE ARCHIVES INT MED, 1909, iv, 331

In experiments which one of us has made, it would appear that those compounds containing a relatively high amount of sulphur are of more importance to the organism than those containing less. Consequently, one might expect that during a time of toxemia when the factors of control were removed a high ratio of sulphur to nitrogen would obtain, while in the stage of convalescence this would be compensated for by a low sulphur-nitrogen ratio. To what extent this is the case will be seen throughout the discussion of the tables.

In some conditions of experimental toxemia, notably in delayed chloroform poisoning, the ratio certainly increases (Howland and Richards).<sup>6</sup>

#### THE NITROGEN PARTITION

##### *Ammonia*

With regard to one constituent of the urine accurate information is very much to be desired. This is ammonia. In view of the important rôle which this product of intermediary metabolism plays in modern theories of acidosis and protein breakdown, it is remarkable that no particular attention has been paid to it in connection with a disease in which the excessive destruction of protein is so well recognized.

Hallervorden,<sup>7</sup> in an examination of the ammonia output in pathological conditions, interpolates the reports of two cases of pneumonia, in one of which, however, the ammonia excretion was examined for two days only. In this case the ammonia excretion was lower on the day of higher fever. In the second case (Fiss) the ammonia rose during the first part of the lysis, and thereafter followed fairly closely the trend of the temperature curve. Hallervorden believes that the increased elimination observed in fever is associated with a retention of fixed bases—potassium and sodium—and that the ammonia is used by the organism in an attempt to protect itself from the loss of these substances. In accordance with the time at which Hallervorden performed his experiments, the Schlosing method was used for the estimation of ammonia. From the accounts he gives, it is quite clear that he had great difficulty in assuring himself of the accuracy of the method. In the course of the present investigations we have had to discard repeatedly specimens of urine on account of commencing decomposition, so that in the work of Hallervorden, and, indeed, through all the work in which the Schlosing method has been used, it is quite possible that variations are due to decomposition occurring during the estimation.

<sup>6</sup> Howland and Richards. *Jour Exper Med.*, 1909, vi, 344.

<sup>7</sup> Hallervorden. *Arch f exper Path u Pharmakol.* 1880, viii, 237.

*Uric Acid*

The intimate relation between the leucocytes and the process of resolution has drawn attention to the purin compounds.

With regard to uric acid, Voges<sup>8</sup> and Friedlichsen,<sup>9</sup> working in von Noorden's clinic obtained normal values for uric acid. Dunin and Nowacek,<sup>9</sup> in an attempt to connect Horbaczewski's theory regarding the connection of the leucocytes with the xanthin base excretion, found an increase in uric acid after the crisis, and this increase, they believe, was due to the breaking down of nuclein compounds during resolution. The increase persisted for two to four days, and was followed by a similar period of lessened output. Only on the seventh day after the crisis did the uric-acid excretion arrive at what they considered a normal value.

Simon,<sup>1</sup> in his interesting study of the autolysis of pneumonia lungs, made under Muller's direction, found free alloxuric bases in the autolysate. One of the most recent investigations in this field is that of Carlyle Pope,<sup>10</sup> who has compared the leucocytosis occurring in various conditions with the elimination of uric acid and xanthin compounds. One case of typhoid and five of pneumonia were studied. In the hyperleucocytosis of typhoid he finds average amounts of uric acid and somewhat greater amounts of xanthin bases. In all cases of pneumonia there was, at certain times, an increase in the xanthin base elimination. There was not a true parallel between the hyperleucocytosis and the increased elimination of xanthin compounds. The increase took place after the disappearance of the hyperleucocytosis and simultaneously with the resolution of the pneumonic exudate.

*Creatinin*

Our information regarding the influence of pathological conditions on the output of creatinin is very scanty. Since the advent of the Folin method, most investigators have very properly confined themselves to the effect of physiological changes on the excretion of the substance. A few, Shaffer,<sup>11</sup> Leathes,<sup>12</sup> and Spriggs,<sup>13</sup> have investigated some of the more important diseases, more especially those connected with disturbances of muscle function.

<sup>8</sup> In von Noorden's Handbuch der Pathologie des Stoffwechsels, 1893, p 278

<sup>9</sup> Nowacek Gaz Lek, 1896, pp 476 517 Cited in Maly Jahresberichte, 1896, xxvi, 769

<sup>10</sup> Pope, C Zentralbl f inn Med, 1899, xx, 657

<sup>11</sup> Shaffer Am Jour Physiol, 1908, xxii, 445

<sup>12</sup> Leathes Jour Physiol, 1907, xxxv, 205

<sup>13</sup> Spriggs Biochem Jour, 1907, ii, 206

In high temperatures, Leathes found that the hyperpyrexia produced in a normal subject by the use of an anlyphoid vaccine caused a rise in the excretion of creatinin. In cases associated with loss of muscular tonus the excretion of creatinin is low relatively to the body weight. In Shaffer's results there is a record of a convalescing typhoid patient in whom the creatinin output was distinctly low. This will be found to agree with the condition in convalescence from pneumonia. After a period of excessive creatinin excretion the values suddenly fell to what must be considered decidedly subnormal. Case 20 of Shaffer's series shows that the creatinin coefficient is very high (10) on the twelfth day of the disease, and falls on the forty-third day to 77. A more striking fall in convalescence is presented by Case 12.

Our own results confirm these findings, except that the transition is much more abrupt (see Case 12, H C.)

#### *Creatin*

The information regarding creatin is much less complete than that of creatinin. We know but few facts which shed light on its pathological significance. Of these the first is its absence from normal urines of subjects on creatin-free diets, and, second, its appearance in the urine of animals exposed to starvation or under-nutrition. It is also found in acute fevers (Ewing and Wolf), in exophthalmic goiter (Shaffer) and in women during post-partum resolution of the uterus (Shaffer).

The significance of these findings is obscure, but one may safely say that at the present time its appearance in the urine denotes either a condition of partial starvation or a pathological state.

#### *Rest Nitrogen*

The question of rest nitrogen is perhaps more complex than any of the previous components, by reason of the number of substances which enter into its composition. In the rest nitrogen in pneumonia are included two classes of compounds which have been closely associated with the disease. One of these is the xanthin bases which could not be determined separately except in a few cases, and whose amount is supposed to be decidedly increased in fevers (Mandel and Lusk).<sup>14</sup>

The other group of compounds consists of the albumoses, or, as they are more frequently called in this connection, the peptones. Maixner<sup>15</sup> found them in pneumonia, mostly during the stage of resolution. Maixner says that he has seen 4 gm of these substances in the twenty-four-

14 Mandel and Lusk Am Jour Physiol, 1906, xvi, 129

15 Maixner Ztschr f klin Med, 1886, xi, 342

large amount of urine. In some of our cases the extreme amounts of undetermined nitrogen led us to examine for albumoses by the method of Devoto.

The composition of the undetermined nitrogen has been discussed by one of us with Ewing<sup>16</sup> in some detail in papers on the clinical significance of the urinary nitrogen, and it is unnecessary to repeat the points of the discussion here, except to point out that in normal subjects the amount of rest nitrogen does not increase in direct proportion to the total nitrogen, so that when one finds an increase one is led to suspect a faulty condition of metabolism, in that the steps leading to the ultimate formation of urea are not properly followed. This aberrance has been called defective desamination. It will be noted that von Jaksch had this idea in mind when he differentiated typhoid fever from pneumonia, regarding the former as a disease in which defective splitting off of ammonia from the protein group played an especial part. In pneumonia this did not occur.

As will be seen, however, amounts of rest nitrogen are obtained in pneumonia which are unequalled in typhoid fever, so that the statement of von Jaksch does not altogether hold. It is true, however, that higher relative values for rest nitrogen are found in typhoid than in pneumonia, but only in daily excretions of nitrogen which are low when compared with pneumonia.

#### *The Sulphur Partition*

The reason for an almost complete lack of accurate data regarding sulphur excretions in pathological conditions arises from the difficulty of the analyses for the clinical investigator. While it is unlikely that the examination of the sulphur partition will give information regarding the oxidative capacity of the organisms as a whole, a study of the sulphates, alkaline and ethereal, will throw light on the processes, putrefactive or otherwise, leading to the formation of ethereal sulphates and at the same time give us some knowledge of the obscure class of compounds making up the neutral sulphur.

As the neutral sulphur compounds must of necessity be included in the rest nitrogen, some conclusions may be drawn regarding the latter as to its content in sulphur-containing substances.

#### *Nitrogen Loss*

Before one can take up the investigation of the individual components of the urine in a disease like pneumonia it is necessary to inquire

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16 Ewing and Wolf. The Clinical Significance of the Urinary Nitrogen. Am Jour Med Sc., 1906, cxxxii, 751.

what the effect of the individual factors entering into the condition is on the nitrogen metabolism as a whole

The most obvious of these are high temperature, dyspnea, and infection, and, as a special factor in pneumonia, the resolution of the pneumonic exudate

With regard to high temperature, most of the estimations of the nitrogen excretion in connection with hyperthermia have been made on cases under the influence of infection, and from these it is difficult to ascertain whether the increase is due to the rise in temperature by itself, or whether the so-called toxic destruction of protein is to be held accountable. Reasoning from purely chemical grounds, it would appear improbable that with a rise in temperature increased nitrogenous decomposition should not take place. We know that the velocity of chemical reactions increases with increments of temperature, and it would be necessary, if the opposite should be found to be the case in pathological conditions, to assume a physiological inhibitory factor interposed, of which, at the present time, there is no evidence. The one experiment in man bearing on the relation of temperature to nitrogen output is that of Linser and Schmid,<sup>17</sup> who experimented with a patient suffering from ichthyosis hystrix. They showed that, on raising the body temperature to 39 C (102 1-102 8 F), which they were able to do by enclosing the patient in a room artificially heated, no increase in nitrogen output took place. If, however, the temperature of the room were further raised so that the body temperature reached 40 (104 F) a decided increase in protein metabolism did take place. From this they inferred, and probably rightly, that they had demonstrated the effect of temperature alone in increasing the nitrogen metabolism. An examination of the increase which Linser and Schmid obtained shows that it is incomparably lower than what is obtained in infectious fevers.

In animals Voit<sup>18</sup> has shown that if the surrounding temperature of fasting animals be raised the nitrogen output is increased. On the other hand, if the animals be protected by the sufficient administration of carbohydrates and fat no comparable increase in the nitrogen metabolism takes place. It is probable that calorimetric investigation of these animals in superheated calorimetric chambers would disclose an increased metabolism falling in this instance, however, on the carbohydrate and fat rather than on the protein, as in the starving animals. As the patients whom we examined were in most cases protected by an amount

17 Linser and Schmid Arch f klin Med, 1904 XXIV, 514

18 Voit Sitzungsber d Gesellsch f Morphol u Physiol Munchen, No 2, 1895

of food sufficient to give almost nitrogen equilibrium in a normal person, the excess output may be set down to factors other than simple hyperthermia alone.

The next factor in the increased nitrogen elimination in these cases is the dyspnea. In this field the investigations of Voit take the first place. In most instances Voit's experiments were carried out on animals in which dyspnea was produced by the mechanical occlusion of the trachea. The results were uniform in showing an increased elimination of nitrogen through the urine as a consequence of hindrance to the gaseous exchange. Voit, however, believes that the increased nitrogen excretion is not primarily due to lack of oxygen, but has its origin in the increased muscular effort of the animal.

Von Noorden<sup>19</sup> reports a case of syphilitic stenosis of the larynx. The amount of nitrogen excreted during the period of fasting was quite within the normal limits.

There remains to be considered the effect of infection on the excretion of nitrogen, and in this field much work has been done both on man and on animals.

It is practically impossible to separate the factors of infection from fever, and therefore the investigators who have worked on the effects of infection have always considered them together. While it is impossible to produce in animals a fever of the long-continued type seen in man, the experiments which have been made in animals are instructive in showing to what extent the protein metabolism may be raised by the combined processes of fever and infection.

May<sup>20</sup> was able to increase the nitrogen elimination in fasting rabbits 51.9 per cent above the normal by infecting these animals with hog-cholera. Stahelin<sup>21</sup> infected dogs with sialia and produced a very marked negative nitrogen balance. In dogs in nitrogenous equilibrium, on about 55 gm of nitrogen, the deficit was 25 gm in a single day, all of which was excreted in the urine. This, it will be seen, is very close to May's 50 per cent increase in rabbits after hog-cholera infection. The knowledge of the effect of fever and infection in man on the excretion of nitrogen is not complete, for it is impossible to determine accurately the state of nutrition of the individual before the infection process began, and one is forced to use as a standard for comparison either results obtained in normal individuals or the metabolism of the same patient during the

19 Von Noorden Handbuch der Pathologie des Stoffwechsels, 1

20 May Ztschr f Biol, 1894 XXX, 1

21 Stahelin Arch f Hyg, 1904, L, 77

period of convalescence. That these are not altogether trustworthy was recognized by Huppert many years ago.

A few experiments have been recorded by Leathes<sup>12</sup> on the nitrogen excretion in aseptic fevers produced by the injection of typhoid vaccine. The fever was neither continuous or excessive, nevertheless a distinct rise in the nitrogen metabolism was observed. Leathes' experiments have been confirmed by Kraus. As Kraus remarks,<sup>22</sup> it is necessary to be extremely careful in any estimate of the nitrogen output in these cases, especially when they are connected with fasting, for the excretions on the third day of a normal fasting subject may vary from 8 to 15 gm.

The problem therefore in the following discussion of the total nitrogen excretion in pneumonia is to ascertain whether the nitrogen eliminated is to be accounted for by the dyspnea and the high temperature, or whether the amount excreted in the twenty-four hours exceeds what may be set down to the two non-infective factors.

If one adds to the high starvation value, viz., 15 gm., that which has been set down to rise in temperature, one still finds in these cases a very considerable amount of nitrogen which must be set down to the infection process alone. It will be observed that in practically all these cases (the exceptions are noted at the proper place) the patients were receiving amounts of nitrogen and units of heat almost sufficient to keep a normal individual in a condition of nitrogen equilibrium.

#### EXPERIMENTAL

The analytical methods employed in this work were those which have been employed by one of us through a series of investigations in normal and pathological metabolism. They were total nitrogen, Kjeldahl, ammonia Folin, urea, Folin, uric acid, Folin-Shaffer, creatinin and creatin, Folin, total sulphur, Folin, total and alkaline sulphates, Folin, chlorids, Volhard, phosphoric acid, uranium acetate.

The urines were preserved with chloroform-thymol-toluol, and were analyzed for ammonia and creatinin as soon as possible after collection. In some instances decomposition had apparently set in during the time they were collected. When this is suspected, it is noted in the tables.

In dividing the cases examined, we have decided to separate arbitrarily the fatal cases from those which terminated in recovery. In some respects a classification of this sort may appear unsatisfactory, but it has the advantage that one is able to correlate the results obtained by a chemical study with the factors which led to a fatal termination. Moreover, in the non-fatal cases we are able to follow the patient through his

<sup>22</sup> In Von Noorden's Handbuch der Pathologie des Stoffwechsels, 1906, 1, 594.

recovery, and from an examination of his metabolism to attempt to make this a part of the basis for clinical prognosis.

In all, 19 cases of pneumonia were examined during longer or shorter periods. Only 14 are reported on, the others do not throw any further light on the condition.

Our original intention was to study the effect of diets containing little or no protein but a fairly large supply of heat in the form of carbohydrate and fat, and to compare this diet with one containing an amount of protein representing about 16 gm of nitrogen. Our reason for doing this was based on a consideration of Benedict and Suranyi's<sup>23</sup> results, in which it was asserted that it was useless to administer large quantities of protein during the nitrogen loss in fever, as the increase in catabolism took place *pari passu* with the nitrogen intake.

Two cases are reported on this non-nitrogenous diet, but it was abandoned on account of the difficulty in inducing the patients to take it. Finally a standard diet was designed with a fair amount of protein, but which was unfortunately not very high in heat units.

It was as follows:

	Amount	Nitrogen	Fat	Carbohydrate	Calories
Milk	1080	5.6	43.0	54.0	765
Crackers	40	0.7	3.6	29.2	158
Boiled rice	120	0.3	0.1	29.0	135
Toast	60	1.1	9.6	36.0	156
Cream	60		13.5	2.4	145
Sugar	90			90.0	360
Total	—	7.7	69.8	240.6	1719

It would have been advantageous to have increased the nitrogen about 5 gm and to have given a great deal more carbohydrate and fat. At the time the work was done by Shaffer had not obtained his very important results on diet in fever, and therefore we are obliged to present these cases with, in some instances, a nitrogen loss which we feel could have been partly avoided with a proper diet.

In some instances eggs were given during convalescence in accordance with the theories of Suranyi and Benedict<sup>23</sup>. This is stated in the notes to the tables.

In taking up the individual cases, we shall discuss the findings in the first case in considerable detail with the intention of using this case as a standard for future comparison. The others will to some extent be referred to the first one in pointing out the differences which occur. In this way a repetition of the findings will be avoided.

<sup>23</sup> Benedict and Suranyi Ztschr f klin Med, 1903, viii, 290

## MILD CASES

CASE 1.—The patient, Z, male, aged 34, alcoholic, had a small area of pneumonia in right upper lobe. He was admitted on the eighth day of the disease, with mild attack, general condition excellent. He was slightly irrational on the night of admission. On the 19th his general condition still excellent, though he began to be delirious. Defervescence began and was completed on morning of 20th. During the 20th, 21st and 22d the patient had an abortive attack of delirium tremens, but his general condition and his pulmonary lesion improved steadily. On the 23d he was comfortable and rational, and from then on to the 29th there was uninterrupted convalescence.

The patient received the higher nitrogen diet, containing 12.1 gm of nitrogen and 1,971 calories. The urine was first examined on the day of the crisis—the seventh day of the disease. On the eighth day the temperature fell to normal. The highest temperature recorded was 104.4, on the day before the examination commenced. The leucocyte count on the seventh day was 14,000.

*Total Nitrogen*.—On the seventh day the total nitrogen excreted was 25.5 gm, and on the eleventh day of the disease, on which a slight post-critical rise occurred, the total nitrogen excretion rose to 30 gm. On the following two days the excretion was each day half that of the day preceding, giving for the last day of the examination 7.1 gm. It is to be noted that with the very high excretion of the eleventh day the patient was physically comfortable, and was well into an uneventful convalescence.

*Amid Nitrogen*.—The percentage of total nitrogen excreted as urea and ammonia is low on the first day of the examination, but rises with defervescence. The highest ratio is obtained during the days of marked fall in temperature. This case would illustrate admirably von Jaksch's statement that pneumonia is a disease in which the catabolism of nitrogen proceeds in the same way as in the normal subject. The ratios of urea and nitrogen are almost as high as one observes in normal subjects. That this, however, is not so with the more toxic cases will be shown later.

*Ammonia Nitrogen*.—A careful examination, not only of this case but of those which follow, leads one to believe that a comparative acidosis occurs. Taking normal individuals with an excretion of 15 gm of nitrogen, the average amount of ammonia nitrogen excreted is about 0.5 gm, and the ratio of ammonia nitrogen to total nitrogen is 3.3 per cent. As will be seen, the amount of ammonia excreted during periods of pyrexia in pneumonia is distinctly higher than this, over 1 gm of ammonia nitrogen being excreted. The ratio is also high—6.7-4.7 per cent of

total nitrogen Both absolutely and relatively the ammonia nitrogen decreases during convalescence

*Urea Nitrogen*—Compared with what one observes in typhoid fever, the ratio of urea nitrogen to total nitrogen is high Compared with normal subjects, it is low The difference in favor of normal urines is small, averaging perhaps 3 to 4 per cent

*Creatinin*—Owing to the large amount of attention which has lately been directed to the output of creatinin in physiological conditions, contributions from the pathological side are at present of considerable interest It is scarcely worth while at this point to review the literature on this subject, except to say it has been found that the daily output of creatinin is practically constant with great changes of diet It is there-

TABLE 1—PROTEIN METABOLISM

Day of Disease	Volume c.c.	Specific Gravity	Reaction *	Albumin	Indican	Total Nitrogen	Albumin Nitrogen	Amid Nitrogen	Per Cent T N	Ammonia Nitrogen	Per Cent T N	Urea Nitrogen	Per Cent T N	Creatinin Nitrogen	Per Cent T N	Creatinin Nitrogen	Per Cent T N
7	1005	1021	†	+++	++++	8.84	1.72	14.57	85.2	1.15	6.7	13.42	78.5	0.64	3.7	0.00	0.0
8	1225	1021	†	+	+	25.50		23.88	93.7	1.22	4.7	22.66	89.0	0.62	2.4	0.00	0.0
9	1025	1021	†	0	+	20.17		18.09	89.7	1.02	5.1	17.07	84.6	0.49	2.5	0.00	0.0
10	No urine received																
11	1605	1023	†	+	++++	30.18		26.93	89.2	0.96	3.2	25.97	86.0	0.77	2.5	0.00	0.0
12	960	1021	†	+	++++	15.45		13.50	87.4	0.36	2.3	13.14	85.1	0.37	2.5	0.13	0.8
13	1205	1010	†	0	+++	7.06		6.46	91.5	0.25	3.5	6.21	88.0	0.19	2.7	0.00	0.0

\* In this and the following tables, an acid reaction is indicated by a dagger (†), and an alkaline reaction +

fore assumed that the creatinin output represents a type of metabolism uninfluenced by the protein intake It has also been found that in patients suffering from certain diseases associated with general loss of muscular tone the ratio of the creatinin excreted to the body weight is decreased, while, conversely, in those conditions in which it is supposed that the metabolism is proceeding at a higher level than normal the creatinin coefficient is increased In starvation, both in men and in animals, it is known that the creatinin output is lower, corresponding with the attempt of the organism to adapt its metabolism to the lessened food intake

In a condition of very great metabolic activity, such as the hyperpyrexia of ammonia, with the loss of 20 or more grams of protein nitrogen on a diet capable of maintaining a normal individual in a state of

nitrogen equilibrium, it might be expected that during this period the endogenous metabolism would be increased, perhaps not *pari passu* with the total increase, but at least sufficiently to make its influence felt on the creatinin output. One would then have the ratio of creatinin nitrogen to total nitrogen decreasing with the rise in total nitrogen output, but the absolute amount of creatinin excreted would be increased. In the majority of cases this happens. During this hyperpyrexia the creatinin output is high as compared with normal individuals. In some instances the highest output is recorded during the stage of resolution. It would appear that at this time not all of the creatinin is derived from endogenous metabolic processes. In pneumonia one has an autolytic process occurring in the lung which may apparently give rise to the excretion of

## PNEUMONIA

	T	S	T N	Total Sulphur	Per Cent S	Alkali Sulphite	Sulphur	Ethereal Sulphur	Sulphate Sulphur	Per Cent S	Neutrial Sulphur	Per Cent S	Neutral S Nitrogen	Rest	Phosphorus	Chlorin	Pulse	Temp ° Fahr
n				Gm		Gm		Gm										
10	7.4	1.19	85.0	1.11	79.3	0.08	5.7	0.21	15.0	13.2	0.43	0.06	96-80	103.6-101.4				
77	7.0	1.52	85.9	1.48	83.6	0.04	2.3	0.25	14.1	46.3	0.43	0.22	100-72	100.0-98.4				
06	5.3	0.94	88.7	0.88	83.0	0.06	5.7	0.12	11.3	8.9	1.29	0.25	88-72	98.6-98.0				
09	6.9	1.94	92.8	1.87	89.5	0.07	3.3	0.15	7.2	7.8	1.75	0.77	72-60	99.4-99.0				
38	5.7	0.77	87.5	0.72	81.8	0.05	5.7	0.11	12.5	9.0	1.01	1.91	66-60	99.8-98.6				
36	5.1	0.27	75.0	0.24	66.7	0.03	8.3	0.09	25.0	26.4	0.38	1.66	76-60	99.0-98.0				

increased amounts of creatinin through the urine. During convalescence the creatinin output is markedly decreased. Not only is the amount diminished, but a comparison with the normal amount excreted will show that it is from one-half to one-third lower than that which is considered normal for a person of average weight. Unfortunately, throughout this entire series it was impossible to take the weights of these patients, so that the creatinin coefficient (the ratio of creatinin to body weight) cannot be given. It is, however, certain that in comparison with the results yielded by normal subjects the creatinin is much higher during hyperpyrexia and falls during convalescence to very low values.

It can scarcely be doubted that after a period of great prodigality of its resources such as occurs in severe toxic conditions associated with high temperature, the organism seeks to conserve its remaining store of

energy to the limit of its capacity. Under these circumstances, not only is the exogenous metabolism used in such a way that tissue repair takes place with great rapidity, as is shown by the remarkable increase in weight which patients often show during convalescence, but the endogenous metabolism, with which we assume creatinin to be associated, is reduced as far as possible. We should, therefore, expect with the onset of convalescence a marked reduction in the creatinin output to occur, a deduction which is borne out by the facts.

*Creatin*.—Quite as much, if not more interest from the standpoint of pathological metabolism is attached to the presence of creatin in the urine. Physiologically, only one condition is known where it appears. This is starvation. On the withdrawal of food, and indeed even in malnutrition, creatin may appear in the urine. This has been shown by Benedict and Dieffendorff and by Cathcart in man, and by one of us in animals. To what its appearance is due it is impossible to say. It is supposed to arise from the breaking down of muscle whose protein is being catabolized. On the other hand, one would scarcely expect it to appear in conditions in which the body was eager to utilize all the available nitrogen-containing compounds possible, for Folin, Klecker and Shaffer, with one of us, have shown that creatin given by mouth on a diet containing little or no protein is utilized as a foodstuff, and not all the nitrogen appears in the urine, but part is stored up in the body. Hence its appearance in the urine in starvation and in these pathological conditions is not connected with starvation alone, for the creatin must be formed at a point when the processes which transform ingested creatin into tissue nitrogen are unable to attack it. Hence it escapes and is excreted in the urine. That it is connected with certain unknown pathological processes seems certain. One finds during the stage of hyperpyrexia that the creatin output is high, despite the fact that the patients are receiving a diet which under normal conditions, both in heat units and nitrogen content, is amply sufficient to protect the urine from the appearance of creatin. Moreover, during convalescence the urine of a patient on the same diet will be perfectly free from creatin. It will be noted that the urine of the patient under discussion, whose case was clinically one of a mild type, contained no creatin, except on a single day in which there was a slight postcritical rise in temperature.

*Uric Acid*.—Compared with the results obtained from normal subjects, the uric acid output throughout this case is high. Folin,<sup>24</sup> in his averages of 30 normal urines, gives the highest output for uric acid nitro-

<sup>24</sup> Folin. Analysis of Thirty Normal Urines. Amer. Jour. Physiol., 1905, XIII, 62.

gen as 0.15, the lowest 0.08 gm, and the average 0.12 gm. During this time the patient was defervescing, the uric acid nitrogen varied from 0.38 to 0.24, and on the day before the postcritical rise 0.55 gm of uric acid nitrogen were eliminated. From that time on the uric acid excretions fell rapidly until on the 25th it was 0.08 gm, the lowest value recorded by Folin. It will be noted that the highest output, 0.55 gm, occurred on the 23d. This is four days after the normal temperature had been reached for the first time, but also on a day on which an excessive nitrogen excretion was obtained. On this day, therefore, it would appear that the autolytic products, resulting from resolution of the lung and containing much nuclein derivatives, were thrown into the circulation and incompletely catabolized.

*Rest Nitrogen*.—One of us in several papers already published has indicated that rest nitrogen plays an important part in the scheme of analysis here followed. In certain disease, notably typhoid fever, and the toxemias of pregnancy, it has been found in the severer stages of the condition that the relative and absolute amounts of the rest nitrogen fractions are increased. This we have been disposed to set down to defective processes of desamination. It is, therefore, interesting to compare the present series of examinations in pneumonia with typhoid fever, as the two have the common factors of high temperature, loss of nitrogen and of body weight. One finds in the severe cases of pneumonia extremely high absolute amounts of undetermined nitrogen, but the relation of rest nitrogen to total nitrogen urea never reached the high value one observes in typhoid fever and eclampsia.

The maximum figure for normal subjects which Folin gives is 0.85 gm and the lowest 0.41 gm, as against, in the mild cases, 1.93 gm. On the other hand, while the ratio for undetermined nitrogen varied in the normal urine of Folin from 2.7 per cent to 5.3 per cent, the values in this case are not a great deal higher. On the first day of the examination, it is true, 8.9 per cent of the total nitrogen was excreted in this form, on the following days the ratio was 2.1 to 7.8 per cent.

One may say, therefore, that, while a large amount of undetermined nitrogen is eliminated, even in the milder cases of pneumonia, the ratio of this fraction of the nitrogen rises but little, if at all. It is, however, significant that when the stage of apyrexia and convalescence has set in, the absolute amounts of undetermined nitrogen are entirely within the limits of what is found for normal subjects. It has been observed on numerous occasions that during the resolution of the lung albumose-like substances have been excreted in the urine, due, as it is thought, to the entrance into the circulation of the products of the autolysis of the lungs. These

would naturally be found in the rest nitrogen fraction. In some cases (Nos 1, 4, 5, 9 and 13) we have tested for the presence of albumoses by Devoto's modification of Hofmeister's method. We have never found such amounts of albumoses as would account for the very high amounts of rest nitrogen found in this case and the following.

*The Sulphur and Its Partition*—As we have already mentioned, the excretion of sulphur and its relation to nitrogen should afford a valuable indication of the type of protein catabolized. It is well known that the relation of sulphur to nitrogen in protein varies between very wide limits. If at a definite time the type of nitrogen catabolized should change, one should have evidence of this change in the varying relation of sulphur to nitrogen in the urine.

If one recalculates the values obtained by Folin in his work on normal urine, one finds a remarkably close agreement between his normal, high, low and average ratios. These are, respectively, 8.3, 8.2 and 8.2, and by dividing the lowest sulphur by the highest nitrogen, and the highest sulphur by the lowest nitrogen, we obtain extreme values of 7.2 and 10 per cent. In the case which we are at present discussing the ratios are undoubtedly lower, varying between 7.4 and 5.1 per cent. This does not always hold, as will be seen in other cases, but from a study of the tables an impression will be gained that at high temperatures the body seeks to retain those proteins containing the higher amount of sulphur, and, for this reason, the ratio of sulphur to nitrogen in the urine falls.

This phenomenon is also to be observed, to a certain extent, in starvation. In this instance, when the body has obvious need of sparing its most valuable protein, and uses up the lesser type, the ratio also falls.

*Sulphate Sulphur*—One has been accustomed for many years to assign the formation of sulphates, particularly the alkaline sulphates, to much the same class of processes as those giving rise to urea, and both have been regarded as indications of the oxidative capacity of the organism. We know that the urea-forming function is not in any sense an oxidation. With the sulphur, however, one must admit that oxidation is the process taking place in transforming the cystin group of the protein molecule into sulphates. This fact Zweifel has used, not with very great success, as a basis to prove a condition of suboxidation occurring in eclampsia.

In the present case, no question of "suboxidation" can be raised, for the ratios of total sulphate sulphur to the total sulphur are high, exceptionally so. The minimum and maximum figures in Folin's results were 84.7 and 89.6 per cent. Here we find ratios between 85.0 and 92.8 per

cent. It is notable that the highest value comes upon the day of highest nitrogen output, when 30.1 gm of nitrogen were excreted.

*Ethereal Sulphate Sulphur*—The values for ethereal do not call for any especial comment in this case. In none of the cases examined are the amounts of ethereal sulphur excreted beyond those found in normal subjects. In Folin's analyses, the absolute amounts of ethereal sulphur excreted varied between 0.076 and 0.100, the average being 0.088. The amounts excreted by this patient were decidedly below this. This is in spite of the fact that the urine showed marked reactions for indican. One of us has previously shown in experimental work in animals that the excretion of ethereal sulphur bears no relation to the test for indican, and this is borne out in cases of pneumonia. It is shown extremely well in this case. One finds a marked test for indican on a day (24th) on which the ethereal sulphur excretion was 0.05 gm, and a weak test on the 21st, on which day 0.06 gm were excreted.

*The Neutral Sulphur*—This fraction of the sulphur deserves especial consideration, for the reason that, apart from being concerned with processes of endogenous metabolism, a comparison of the neutral sulphur with the undetermined nitrogen should throw light on the composition of the latter. In the group of compounds designated as rest nitrogen, there are estimated the purin compounds, excluding uric acid, the proteic acids of Bondzynski and his coworkers, the amino-acids, indol and skatol compounds, etc. The compounds which interest us here are the proteic acids which contain sulphur, and hence are common to the rest nitrogen and neutral sulphur groups. Most of the albumoses also contain sulphur and are hence in these two classes. As has been mentioned, albumoses are found in the urine in pneumonia, particularly during the stage of resolution, and Gawinski<sup>25</sup> has found that the proteic acids are found increased in certain pathological conditions.

A consideration of the relation of neutral sulphur to undetermined nitrogen should enable us to determine whether at certain periods of the disease relatively more sulphur-containing compounds of unknown character are excreted.

In the case under examination it will be seen that the ratios vary considerably. Starting with a ratio of neutral sulphur x 100 to rest nitrogen of 13.2 on the day of a beginning crisis, the ratio suddenly rises to 46.3 a phenomenon which would correspond with Gawinski's findings of increased oxyproteic acids. Thereafter the ratio falls to the neighborhood of 10 per cent (8.9, 7.8, 9.0), and on the last day of the exami-

<sup>25</sup> Gawinski Ztschr physiol Chem., 1908, LIII, 462. See also Ginsberg Beitr z chem Physiol u Path (Hofmeisters), 1907, v, 411.

nation rises to 26.4 per cent. In some of the following cases much greater differences will be found in the ratios between the neutral sulphur and undetermined nitrogen, and one case will furnish an example of as much sulphur in neutral form being excreted as test nitrogen.

*Phosphorus*.—In connection with the breaking down of nuclear compounds and their metabolism, the phosphorus elimination shows a marked rise during the latter part of the crisis. Not only is the rise an absolute one, but the ratio to total nitrogen is increased over 300 per cent. It would appear, from this case at least, that during the stage of hyperpyrexia phosphorus is retained by the body in much the same way as is the chlorin. This agrees entirely with Gouraud's statement.<sup>26</sup> In Gouraud's case the commencing increase in the chlorin excretion preceded that of phosphorus by twenty-four hours.

TABLE 2.—PROTEIN METABOLISM

Day of Disease	Volume c.c.	Specific Gravity	Retention	Albumin	Indican	Total Nitrogen	Gm	Amid Nitrogen	Gm	Per Cent T N		Ammonia Nitrogen	Gm	Per Cent T N		Urea Nitrogen	Gm	Per Cent T N		Creatinin Nitrogen	Gm	Per Cent T N		Uric Acid Nitrogen	Gm		
										Per Cent	T N			Per Cent	T N			Per Cent	T N			Per Cent	T N				
2	832	1024	†	0	0	15.91	14.11	88.7	1.09	6.9	13.02	81.8	0.32	20	0.25	1.6	0.04										
3	628	1025	†	0	0	15.14	13.43	88.7	0.69	4.5	12.74	84.2	0.28	19	0.23	1.5	0.04										
4	1110	1023	‡	++	0	27.57	24.84	90.2	2.14	7.8	22.70	82.4	0.52	19	0.19	0.7	0.06										
5	635	1025	‡	+	0	13.69	11.92	87.2	2.73	20.0	9.19	67.2	0.30	22	0.22	1.6	0.04										
6	535	1021	†	0	0	10.10	8.51	84.1	0.64	6.3	7.87	77.8	0.37	37	0.09	0.9	0.02										
7	570	1016	†	0	0	6.82	5.63	82.5	0.59	8.6	5.04	73.9	0.31	45	0.06	10	0.03										

During the first period of the examination of the present case but 0.06 gm of chlorin were excreted. This was followed by a rise to 0.22 gm, while the excretion of phosphorus remained constant, rising on the succeeding day. Gouraud was not able to make out a coincidence between the excretion of chlorin and of phosphorus, nor, as will be seen from our results have we.

CASE 2.—The patient, T. E. S., male, aged 23, non alcoholic, was admitted on the third day of the disease (January 26) with a mild attack of right lower lobe pneumonia. His general condition was excellent, he never gave the impression of being ill. February 2 the temperature began to fall, patient slept well, ate well, and was comfortable, same on the 28th, with temperature two degrees lower. On the 29th temperature reached normal. Convalescence from then on was uninterrupted.

The examination of the metabolism of this patient was commenced during the crisis. The temperature of the patient was falling already on the day of admission.

This case differs from the preceding in that the increase in nitrogen in Case 1 was not arrived at until the third day after the temperature was normal. There is also to be noted the marked fall in nitrogen excretion at the end of the experiment, when the patient came into what was practically nitrogenous equilibrium on a diet on which but a few days before he had lost nearly 20 gm of nitrogen.

*Creatinin and Creatin*—In accordance with the clinical findings of a not excessively toxic condition the creatinin elimination is not high but a not inconsiderable amount of creatin is excreted, the results showing an almost constant daily quantity throughout the disease. On the

#### 2, MILD PNEUMONIA

Total Sulphur Gm	T	S	N	Total Sulphate Sulphur		Alkali Sulphite Sulphur	Per Cent T S	S	Ethereal Sulphate Sulphur	Per Cent T S	S	Neutral Sulphur Gm	Per Cent T S	S	Chlorin Gm	Per Cent T S	S	Phosphorus	Neutral S Nitrogen	Rest	Pulse	Temp ° F.m
				T	S																	
1.45	9.1	1.27	87.6	1.24	85.5	0.03	2.1	0.18	12.4	0.60	1.10	15.1	100-88	103.6-101.9								
1.26	8.3	1.07	84.9	1.03	81.7	0.04	3.2	0.19	15.1	0.19	0.30	16.3	120.92	101.4-100.5								
2.23	8.1	1.84	82.5	1.78	79.8	0.06	2.7	0.39	17.5	0.27	0.39	19.9	110.92	100 - 98.4								
1.10	8.0	0.86	78.2	0.82	74.5	0.04	3.7	0.24	21.8	0.85	0.62	19.8	96.80	99.8- 99.0								
0.70	6.9	0.54	77.2	0.48	68.6	0.06	8.6	0.16	22.8	0.71	0.53	14.4	96.78	99.4- 98.4								
0.55	8.1	0.43	78.2	0.37	67.3	0.06	10.9	0.12	21.8	0.65	0.42	15.2	104.80	100 - 98.4								

day of highest nitrogen elimination, the creatinin was very high for this patient (0.52 gm), falling on the subsequent days to the original excretion 0.31 gm. As probably on this day a large amount of nitrogen, due to the resolution of the lung, was thrown into the circulation, it is suggestive that a part of this creatinin was derived from the products of autolysis.

It will be noted that while the creatin output is high in the first part of the examination, no increase takes place with increase in total nitrogen and, following this, the substance all but disappears from the urine.

*Uric Acid*—The uric-acid excretion in this case is somewhat anomalous for the amount excreted during the disease is, if anything below that found in normal subjects and no rise takes place in its excretion during the period in which a very large amount of nitrogen is being

catabolized During the period from the 28th day to the 31st, the leucocyte count fell from 24,100 to 10,000 per cubic millimeter The remaining point in connection with this case is the close relation which exists between the neutral sulphur and the undetermined nitrogen No such variation takes place as was found in Case 1 The values in the present case lie between 15 per cent and 20 per cent , while in the former case a variation occurs between 78 per cent and 46.3 per cent One may conclude in this case that with regard to their sulphur content the substances which were being excreted as undetermined nitrogen were fairly constant in composition

CASE 3—The patient, B , male, aged 45, three days before admission had pain in the right side with shortness of breath and very slight cough He did not have

TABLE 3—PROTEIN METABOLIS

Day of Disease	Volume c c	Specific Gravity	Reaction	Albumin	Indican	Total Nitrogen	Amid Nitrogen	Per Cent T N	Ammonia Nitrogen	Per Cent T N	Urea Nitrogen	Per Cent T N	Creatinin Nitrogen	Per Cent T N	Creatinin Nitrogen	Per Cent T N	Urie Acid	Nitrogen	Per Cent T N
3	1530	1021	+	0	+	22.80	20.06	88.0	1.66	7.3	18.40	80.7	0.78	3.4	0.0	0.30	1.4		
4	940	1018	+	+	0	9.88	8.25	83.6	0.45	4.6	7.80	79.0	0.43	4.4	0.0	0.17	1.7		
5	650	1019	-	+	+	7.96	6.23	78.3	0.76	9.5	5.47	68.8	0.45	5.8	0.0	0.10	1.2		
6	390	1023	+	+	+	5.50	4.25	77.3	0.54	9.8	3.71	67.5	0.36	6.5	0.0	0.10	1.8		
7	380	1022	+	0	+	5.45	4.24	77.8	0.44	8.1	3.80	69.7	0.40	7.8	0.0	0.10	1.9		
8		1030	-	0	+			77.3		7.0		70.3		7.6	0.0				
9	1370	1006	+	0	+	5.78	5.10	88.2	0.71	12.2	4.39	76.0	0.37	6.4	0.0	0.07	1.2		
10	3680	1001	+	0	0	4.53	3.83	84.5	0.85	18.7	2.98	65.8	0.37	8.2	0.0	0.11	2.4		

a chill, but sweated at night Examination showed over middle and right middle lobes anteriorly and laterally very loud pleuritic friction sounds, over right lower lobe posteriorly and laterally marked dulness, diminished fremitus and diminished distant breathing Diagnosis, pleurisy with effusion The patient was given the non-nitrogenous diet, consisting of malted starch, cream and sugar, and 6 gm of sodium chlorid

This third case, which serves to a certain extent for comparison with the foregoing two, is one of tuberculous nature with continued high temperature As will be seen from the records, the temperature was seldom under 103, and for a greater part of the time of the examination 104 With this temperature there was no hyperleucocytosis, and the Widal reaction was negative Before the examination, 1,000 c c of fluid had been taken from the chest

This patient is of interest also from the dietetic side, for he was given a nearly non-nitrogenous diet,<sup>27</sup> consisting of malted starch<sup>28</sup> and cream. The number of calories given were 2,500. The nitrogen content of the food was about 1 gm. In addition, 6 gm of sodium chloride were administered.

On the first day of the examination 22.8 gm of nitrogen were excreted in the urine, representing at least that amount of nitrogen loss from the body. Thereafter the amount fell 9.8, and finally to 4.5 gm.

This lower amount is what one may obtain in a normal individual with the same diet, so that even with the high temperature of this patient (103.6 on the sixth day) an output of 4.53 gm cannot be considered as the indication of a very definite toxic destruction of protein.

#### CASE 3, MILD PNEUMONIA

Percent Total Sulphur Gm	T S Gm	T N Gm	Total Sulphur Sulphur Gm	Alkali Sulphate Sulphur Gm	Per Cent T S Per Cent Sulphur Gm	Ethereal Sul- phate Sulphur Gm	Per Cent T S Per Cent Sulphur Gm	Neutral Sulphur Gm	Pet Cent T S Pet Cent Sulphur Gm	Chlorin	Phosphorus	Neutral S Rest Nitrogen Gm	Pulse	Temp ° Fahr	
7.2	1.92	8.4	1.41	73.4	1.33	69.3	0.08	4.1	0.51	26.6	6.96	0.91	30.7	98-84	103.6-103.0
10.3	0.70	7.1	0.58	82.9	0.53	76.8	0.05	6.2	0.12	17.1	5.18	0.38	11.7	108.80	103.6-102.8
11.7	0.65	8.2	0.36	55.4	0.30	46.2	0.06	9.2	0.29	44.6	2.71	0.49	24.5	104-88	103.4-102.0
14.4	0.46	8.4	0.22	47.8	0.19	41.3	0.03	6.5	0.24	52.2	1.61		30.4	108-98	103.8-102.8
13.5	0.51	9.3	0.22	43.1	0.18	35.3	0.04	7.8	0.29	56.9	0.53		40.8	104-96	103.4-101.2
15.1														104-82	102.8-102.0
4.2	0.47	8.1	0.22	47.1	0.20	43.3	0.02	3.8	0.25	52.9	3.49	0.22	104.2	110-88	102.4-101.0
4.9	0.48	10.6	0.19	39.6	0.14	29.1	0.05	10.5	0.29	60.4	4.68	0.21	131.8	100-84	103.2-99.8

This case will later be compared with that of a highly toxic pneumonia patient (Case 12), who was placed for a few days on this diet. The most striking differences in the reaction of the two cases to this diet will be at once apparent.

Throughout this case was observed a very close agreement with the normal figures of Folin. Moreover, no creatin is found at any time in

27 Folin Am Jour Physiol, 1905, xiii, 73.

28 The malted starch was made by taking arrowroot starch, heating with water in a double boiler and after cooling to 70 C allowing an extract of malt to act on the starch in order to effect a partial conversion into maltose. The resulting mixture of maltose and starch is fluid while hot and semi-solid when cold. When flavored with lemon or vanilla it is readily taken by patient.

this series of analyses, despite the fact that during the examination the patient received practically no protein

On the last day on which the urine was examined, a marked polyuria will be noted, due to the administration of 1,000 c.c. of "white drink"

The flushing out of the system by the very large quantity of urine passed did not have any influence either on the excretion of nitrogen or on the undetermined nitrogen

CASE 4.—The patient, L. B., male, aged 18, was admitted on the fifth day of the disease (April 26) with a mild attack of central pneumonia, coming to the surface of the lung at the lower right lobe in small area. On the 27th the patient

TABLE 4—PROTEIN METABOLISM

was comfortable, condition good. A precritical rise of temperature to 104 occurred on this day, followed on the 28th by defervescence during the day, which was completed on early morning of the 29th. On the 28th he was comfortable, condition excellent, on the 29th, lung was resolving, which was completed by May 1. Convalescence was uninterrupted, patient discharged May 10.

In this case the crisis occupied about thirty-six hours for its completion, and in order to study the effects of an uninterrupted convalescence the examinations of the urine were continued over nine days, during which time the temperature was normal. One finds the nitrogen and sulphur excretion steadily decreasing, but the total output is high, never decreasing below 9.89 gm. This is in marked contrast with the case of pleurisy (Case 3, B) which we have just discussed.

On the eleventh day of the disease there is a marked rise in the nitrogen excretion to 28.9 gm, unaccompanied by rise in temperature, pulse or any unusual clinical signs. Unquestionably, at this point the products of the autolysis of the pulmonary exudate were suddenly thrown into the circulation. On the day preceding, warning of this was given by a rise in total nitrogen from 9.8 to 13.9 gm. This rise is not accompanied by any special features in the distribution of the nitrogen, except in two respects, a marked rise in the excretion of creatinin, and the advent of a comparatively large amount of creatin in the urine. Unexpectedly, the uric-acid excretion is not affected, although on this day a

## SE 4, MILD PNEUMONIA

	Per Cent T N	Total Sulphur Gm	T S	Total Sulphur Gm	Per Cent T S	Alkali Sulphur Gm	Per Cent T S	Ethereal Sul- phate Sulphur Gm	Per Cent T S	Neutral Sulphur Gm	Per Cent T S	Neutral S Nitrogen	Rest Sulphur Gm	Phosphorus Gm	Chlorin Gm	Pulse	Temp ° Fahr
21	17.0	1.42	5.7	1.18	83.1	1.12	78.9	0.06	4.2	0.24	16.9	5.7	1.22	1.96	112.84	104.0-101.0	
35	4.9	1.20	6.9	0.98	81.7	0.94	78.3	0.04	3.4	0.22	18.3	25.9	1.30	2.45	96.72	101.8-100.0	
34	4.4	1.49	6.9	1.28	85.9	1.25	83.9	0.03	2.0	0.21	14.1	22.3	1.75	0.88	76.64	99.2- 98.4	
37	3.2	1.20	6.8	1.04	86.7	0.98	81.7	0.06	5.0	0.16	13.3	28.1	1.76	1.79	64.60	99.0- 98.2	
37	2.4	1.02	6.3	0.92	90.2	0.86	84.3	0.06	5.9	0.10	9.8	27.0	1.33	3.35	64.60	99.0- 98.0	
82	4.9	1.04	6.2	0.94	90.4	0.87	83.7	0.07	6.7	0.10	9.6	12.2	1.49	2.31	76.64	98.6- 98.0	
32	2.4	0.80	6.0	0.70	87.5	0.67	83.8	0.03	3.7	0.10	12.5	31.2	1.08	1.23	80.64	98.4- 98.2	
24	2.4	0.62	6.3	0.53	85.5	0.49	79.0	0.04	6.5	0.09	14.5	37.5	0.62	1.08	72.64	98.4- 98.0	
46	3.3	1.03	7.4	0.94	91.3	0.91	88.3	0.03	3.0	0.09	8.7	19.5	1.22	2.30	68.64	98.4- 98.0	
10	3.7	2.13	7.3	1.93	90.6	1.80	84.5	0.13	6.1	0.20	9.4	18.2	2.56	4.55	84.64	98.8- 98.0	
14	1.7	0.63	7.6	0.54	85.7	0.51	81.0	0.03	4.7	0.09	14.3	64.3	0.82	0.32	92.72	99.0- 98.4	
16	2.1	0.57	7.0	0.51	89.5	0.48	84.2	0.03	5.3	0.06	10.5	37.5	0.66	0.57	96.92	99.0- 98.4	

very large amount of phosphorous is eliminated. The reason for this is obscure. On this day, and the following day, the ratios of sulphur to nitrogen undergo another change. Where for some time previously the ratios varied from 6.0 to 6.3 the ratio is now 7.4 to 7.6, indicating with this rise in the ratio that a type of protein is being catabolized which contains considerably more sulphur.

Regarding the ratio of neutral sulphur to rest nitrogen some very interesting facts are disclosed bearing on the composition of these substances.

The high elimination of nitrogen at the crisis is attended with the excretion of substances of unknown composition, which are relatively poor

## PROTEIN METABOLISM IN PNEUMONIA

in sulphur. The character of these substances changes directly after the crisis, when substances comparatively rich in sulphur are excreted.

The high postcritical rise in nitrogen excretion produces a group of nitrogenous substances which for two days are practically constant in

TABLE 5—PROTEIN METABOLISM IN

Day of Disease	Volume c.c.	Specific Gravity	Reaction	Albumin	Indican	Gm	Total Nitrogen	Gm	Amid Nitrogen	Per Cent T N	Gm	Ammonia Nitrogen	Per Cent T N	Gm	Urea Nitrogen	Per Cent T N	Gm	Creatinin Nitrogen	Per Cent T N	Gm	Creatinin Nitrogen	Per Cent T N	Gm	Uric Acid Nitrogen	Per Cent T N
7	625	1021	†	0	+++	13.44	12.03	89.5	0.47	3.5	11.56	86.0	0.27	2.0	0.00	0.0	0.23	1.7	0.00	0.0	0.14	1.9	0.07	0.06	
8	345	1024	†	0	+++	7.21	6.20	86.0	0.31	4.3	5.89	81.7	0.13	1.8	0.00	0.0	0.14	1.9	0.00	0.0	0.00	0.0	0.07	0.06	
9	390	1028	†	0	+++	9.00	7.93	88.1	0.37	4.1	7.56	84.0	0.16	1.8	0.00	0.0	0.21	1.6	0.00	0.0	0.21	1.6	0.07	0.06	
10	855	1021	†	0	+++	12.70	11.37	89.5	0.48	3.8	10.89	85.7	0.29	2.3	0.00	0.0	0.21	1.6	0.00	0.0	0.14	1.9	0.07	0.06	

their undetermined nitrogen-sulphur composition, the ratio standing at 5 to 1. This is followed by an exceedingly low excretion of rest-nitrogen compounds very rich in sulphur.

TABLE 6—PROTEIN METABOLISM IN

Day of Disease	Volume c.c.	Specific Gravity	Reaction	Albumin	Indican	Gm	Total Nitrogen	Gm	Amid Nitrogen	Per Cent T N	Gm	Ammonia Nitrogen	Per Cent T N	Gm	Urea Nitrogen	Per Cent T N	Gm	Creatinin Nitrogen	Per Cent T N	Gm	Creatinin Nitrogen	Per Cent T N	Gm	Uric Acid Nitrogen	Per Cent T N	
2	1000	1018	‡	+	0	17.00	14.90	87.7	1.30	7.6	13.60	80.0	0.48	2.8	0.00	0.0	0.03	0.2	0.00	0.0	0.09	1.2	0.02	0.3	0.00	0.0
3	520	1019	‡	++	0	7.39	6.07	82.1	2.81	38.0	3.26	44.1	0.12	1.6	0.09	1.2	0.02	0.3	0.00	0.0	0.09	1.5	0.03	0.2	0.00	0.0
4	885	1016	‡	0	0	12.80	10.76	84.1	1.81	14.2	8.45	69.9	0.14	1.1	0.34	2.7	0.03	0.2	0.00	0.0	0.34	1.5	0.28	1.2	0.05	0.2
5	1250	1017	‡	0	0	22.80	20.00	87.7	0.81	3.6	19.19	84.1	0.25	1.1	0.34	1.5	0.28	1.2	0.00	0.0	0.34	1.5	0.28	1.2	0.05	0.2
6	1545	1019	‡	0	0	24.72	21.48	86.9	6.63	26.8	14.85	60.1	0.23	0.9	0.35	1.4	0.05	0.2	0.00	0.0	0.35	1.4	0.05	0.2	0.00	0.0

It is to be hoped that further work in the more detailed analysis of the rest nitrogen in conditions such as pneumonia will reveal the cause of this very interesting change in relationship.

## MODERATELY SEVERE CASES

CASE 5.—The patient, W. W., male, aged 25, not alcoholic, had right upper lobar pneumonia. He was admitted April 11 with frank moderately severe attack. On the third day of disease temperature was 104.5 F., pulse 102, respiration 36,

during the night The patient's general condition improved, and on the 12th he was in good condition On the 13th he was slightly delirious during the day and night, but during the 14th he again improved, and on the 15th, the seventh day of the disease, he was comfortable and defervesced The 16th, 17th, 18th and 19th were days of a rapid and good convalescence

### 5. MODERATELY SEVERE PNEUMONIA

This case ended by crisis, with a marked postcritical rise on the day following. This day is the one on which the urine was first examined. This case does not differ markedly from the preceding case, except that

#### CASE 6, MODERATELY SEVERE PNEUMONIA

	Gm	Per Cent	T	N		T	S	T	N		Total Sulphur		Total Sulphate	Sulphur		Rest Nitrogen
	Gm				Gm					Gm			Gm			Per Cent T N
159	9.4	1.26	7.4	0.96	76.0	0.93	73.3	0.03	2.7	0.30	24.0	18.9	0.66	0.24	116- 96	103.8-103.4
109	14.8	0.82	11.1	0.67	81.1	0.65	79.0	0.02	2.1	0.16	18.9	14.7	0.19	0.22	112-100	103.0-100.8
153	11.9	1.38	10.8	1.17	84.9	1.13	82.0	0.04	2.9	0.21	15.1	13.7	0.29	0.11	120-100	103.2-100.4
193	8.5	1.15	6.4	1.20	82.8	1.15	79.4	0.05	3.4	0.25	17.2	13.0	0.37	0.38	106- 92	99.4- 98.2
261	10.6	1.55	6.3	1.17	75.5	1.13	72.6	0.04	2.9	0.38	24.5	14.5	1.34	0.75	92- 80	100.8- 99.4
															Pulse	Temp ° Fahr

the ratios for amid and urea nitrogen are somewhat higher. The ammonia is low, both relatively and absolutely, as is also the creatinin

In this case one sees very clearly the retention of phosphorus and its subsequent elimination, after the temperature has reached normal

CASE 6.—The patient, T. R., male, aged 46, moderately alcoholic, with history of syphilis, was admitted on fifth day of disease, though the lung was not fully consolidated. Temperature, 5 p.m., was 105 F., pulse 106, respiration 34. Consolidation developed during the night of admission in the right lower lobe. On

the 21st patient was comfortable except for pain on coughing, condition good, moderately severe attack. On the 22d, condition was slightly better, on the 23d, condition showed continued improvement, and defervescence occurred during the night, on the 24th, improvement continued and resolution of lung began, on the 25th, resolution continued with marked general improvement, on the 26th, the patient was convalescent, lung resolved rather slowly.

This case differs from the preceding in that the defervescence was spread over at least four days. The analyses of the urine of the patient are complicated by the fact that on one day at least the urine was contaminated, and all the specimens but one were alkaline, so that the relative values for urea and ammonia are uncertain.

TABLE 7—PROTEIN METABOLISM IN

Day of Disease	Volume c.c.	Specific Gravity	Reaction	Albumin	Indican	Total Nitrogen			Per Cent T N	Ammonia Nitrogen			Per Cent T N	Urea Nitrogen			Per Cent T N	Creatinin Nitrogen			Per Cent T N	Uricle Acid Nitrogen		
						Gm	Gm	Gm		Gm	Gm	Gm		Gm	Gm	Gm		Gm	Gm	Gm		Gm	Gm	Gm
4	1176	1023	†	++	++	25.66	22.60	88.1	0.91	3.6	21.69	84.5	0.58	2.3	0.34	1.4	0.26							
5	1150	1021	†	++	+++	19.37	17.16	88.6	0.81	4.2	16.35	84.4	0.54	2.8	0.27	1.4	0.32							
6	1100	1025	†	+	++++	22.48	20.08	89.3	0.74	3.3	19.34	86.0	0.54	2.4	0.20	0.9	0.35							
7	700	1024	†	0	++++	14.76	13.08	88.6	0.83	5.6	12.25	83.0	0.48	3.2	0.00	0.0	0.24							
8	560	1025	†	0	++	11.50	10.08	87.7	0.97	8.5	9.11	79.2	0.34	2.9	0.07	0.6	0.17							
9	No specimen received																							
10	710	1028	†	0	++++	15.35	13.64	88.9	0.68	4.4	12.96	84.5	0.55	3.6	0.00	0.0	0.31							
11	840	1027	†	0	++++	17.85	16.05	89.9	0.95	5.3	15.10	84.6	0.57	3.2	0.08	0.5	0.30							
12	960	1028	†	0		20.96	18.96	90.5	1.04	5.0	17.92	85.5	0.61	2.9	0.00	0.0	0.32							

The case is of interest in showing postcritical rise in the elimination of nitrogen, on the 23d day, only 12.8 grams of nitrogen were excreted, while on the 25th day 24.2 grams were eliminated.

Very high ratios of total sulphur, total nitrogen were obtained on the second and third days of the examination, viz., 11.1 and 10.8, and in this respect this patient differs from the preceding ones, in which the effort of the individual to spare his sulphur at the beginning of the illness is made plain by the low ratio obtaining at that time.

CASE 7.—The patient, F—t, male, aged 26, non alcoholic, was admitted on the first day of the disease, May 12. On admission temperature was 103, pulse 104, respiration 52. There were severe pain and dyspnea from pleurisy. The lung was in a stage of congestion in left lower lobe, the patient moderately sick. General condition was good on the 13th and 14th, though temperature was 104.5 F., pulse 120, respiration 24 during both afternoons, signs in chest seemed more those of fluid than consolidation. Chest was tapped with negative result. Patient was not so well during night of the 14th, decidedly improved on the 15th, mod-

erately sick during the 16th. He continued to improve, and during the 17th to the 24th slowly but steadily improved. The temperature fell by lysis, the lung beginning to resolve on the 21st.

This case shows the course of a very protracted lysis, the temperature not reaching normal during the course of the examination. The diet during the examination contained four eggs, in addition to the amount the other patients received, bringing the nitrogen to 12 gm.

The first respect in which this case differs from the preceding is the constantly high excretion of nitrogen. The fluctuations are great, it is true, varying between 25.6 and 11.5 gm., but no steady decrease is

#### CASE 7, MODERATELY SEVERE PNEUMONIA

	Rest Nitrogen Gm	Per Cent T N Gm	Total Sulphur Gm	T S T N Gm	Total Sulphate Gm	Per Cent S Gm	Alkali Sulphate Sulphur Gm	Per Cent S Gm	Ethereal Sulphate Sulphur Gm	Per Cent S Gm	Neutral Sulphur Gm	Per Cent S Gm	Neutral S Nitrogen Rest Gm	Phosphorus Cholin Gm	Pulse	Temp ° Fahr	
0	1.88	7.2	1.66	6.5	1.28	77.1	1.22	73.5	0.06	3.6	0.38	22.9	20.1	0.62	1.06	116-92	103.8-102.0
7	1.08	5.5	1.37	7.1	1.10	80.3	1.01	73.7	0.09	6.6	0.27	19.7	25.0	0.68	0.83	120-96	103.0-101.6
6	1.31	5.8	1.62	7.2	1.33	82.1	1.25	77.2	0.08	4.9	0.29	17.9	22.1	0.65	0.66	100-92	102.2-100.4
6	0.96	6.6	1.02	6.9	0.84	82.4	0.77	75.5	0.07	6.9	0.18	17.6	18.8	0.51	0.59	104-92	102.4-100.2
5	0.84	7.3	0.76	6.6	0.64	84.2	0.60	79.0	0.04	5.2	0.12	15.8	14.3	0.55	0.44	116-88	102.0-100.2
	0.85	5.5	1.17	7.6	0.97	82.9	0.90	76.9	0.07	6.0	0.20	17.1	23.5	0.97	1.41	108-96	102.2-99.4
	0.85	4.7	1.33	7.4	1.15	86.5	1.08	81.2	0.07	5.3	0.18	13.5	21.2	1.13	1.82	108-100	102.6-100.6
	1.07	5.1	1.48	7.1	1.35	91.2	1.25	84.5	0.10	6.7	0.13	8.8	12.2	1.46	1.61	96-80	101.0-100.0

observed in the elimination. It is instructive, however, to compare this case with Case 3, in which the temperature had a course similar to this except that the temperature was uniformly almost a degree higher. There we concluded we were dealing with a tuberculous pleurisy, with little or no toxic destruction of protein. Here, if one may judge from the nitrogen excretion, the amount of protein destroyed is excessive.

In accordance with what appears to us to indicate excessive metabolism due to the action of the toxins one finds higher absolute amounts of creatinin with a fall at a period coinciding with lower temperature. With this high creatinin excretion, we find associated a large amount of creatin, reaching on the first day the very unusual amount of 0.34 gm.<sup>27</sup>

27 It will be instructive to note the explanation of this high creatin output in cases of typhoid which has been offered by Ewing and Wolf (THE ARCHIVES INT MFD, 1909, IV, 336). A similar explanation will satisfy the difference which one observes in the total nitrogen and creatin output in Cases 3 and 7 of this series.

With the progress of the case, we here find a fall in creatinin and a subsequent rise and, what is of more interest, the practically complete disappearance of creatin from the urine. This case is also marked by the larger amount of uric acid excreted, a circumstance which seems also to point to excess in nuclear destruction. This is also partly borne out by the fact that the phosphorus excretion in this case is uniformly high, in one day, the last of the examination, 146 gm of phosphorus being excreted.

The next case which we present, while incomplete serially, gives the nitrogen metabolism occurring during a crisis in which the temperature fell in twenty-four hours from 106 to 98.2

CASE 8.—The patient, P. F., male, aged 34, with alcoholic history, was admitted sixth day of disease, February 7, moderately sick, with a small central patch of pneumonia in the left upper lobe, symptoms in excess of amount of lung involved, with mild alcoholic hallucinations. In spite of high temperature (106), and pulse of 120, patient did not impress one as being very ill during the 18th and 19th. On the 18th consolidation spread through upper lobe. Rapid defervescence secured on the 20th, and marked improvement, and on the 21st, convalescence. Lung cleared by the 25th.

The first collection of urine was not made quantitatively. On the day on which the crisis commenced, the total nitrogen was comparatively low, only 9.2 gm being excreted. During the following twenty-four hours the nitrogen excretion had risen to 24.7 gm. With this increase the uric acid, previously excreted to the amount of 0.05 gm, rises to six times that amount. The undetermined nitrogen also increased in exactly the same ratio.

The crisis was followed by a slight postcritical rise, during which no more specimens of urine were examined. The excretion of nitrogen on this day was even higher, rising to 26.1 gm. In both these days the low ratio of amid nitrogen, and the high undetermined nitrogen, led one to conclude that through this period the products of autolysis were being excreted in such amounts as to escape the catabolic processes leading to ammonia and urea.

#### SEVERE CASES

The following group of cases are those of patients clinically characterized as severely ill.

CASE 9.—The patient, C., male, aged 27, non alcoholic, with history of syphilis, four years previously, was admitted April 22 with right lower lobe pneumonia, eighth day of disease. On April 23, temperature was 104.8° F., pulse 104, respiration 40, patient was severely sick and delirious, general conditions not good. On the 24th, he was still severely sick. On the 25th, the patient began to improve, but was still delirious. On the 26th, he was much improved in general.

TABLE 8—PROTEIN METABOLISM IN CASE 8, MODERATELY SEVERE PNEUMONIA

Day of Disease	Volume cc	Specific Gravity	Reaction	Albumin	Indicau	Total Nitrogen	Ammonia Nitrogen	Per Cent T N	Urea Nitrogen	Per Cent T N	Creatinine Nitrogen	Per Cent T N	Urine Acid Nitrogen	Per Cent T N	Rest Nitrogen	Per Cent T N	Pulse	Temp ° Fahr
8	1025	† +	Gm	95.6	6.6	89.0	3.0	0.0	0.0	0.2	1.2	126.	92	105.8	102.8			
9	390	1027	† ?	9.25	8.46	91.5	0.43	4.7	8.03	86.8	0.30	3.2	0.00	0.0	0.05	0.5	0.44	4.8
10	1045	1024	† ?	24.70	21.40	86.6	1.67	6.8	19.73	79.8	0.56	2.3	0.00	0.0	0.31	1.3	2.13	9.8
13	1125	1020	†* +	26.16	23.00	87.8	1.30	5.0	21.70	82.8	0.54	2.1	0.13	0.5	0.06	0.2	2.43	9.3
																		96-70
																		100.0-99.0

\* Slightly alkaline ? Trace

condition, though still delirious, defervescence began On the 27th, defervescence completed, general condition excellent, though patient was delirious at night On the 28th, he was convalescent, on the 29th, lung cleared

This case is distinguished from those which precede by a considerable amount of albumin in the urine, indicating the effect of the toxic condition on the kidneys On the other hand, the toxemia does not appear to have led to a very marked destruction of protein, for at no point in the

TABLE 9—PROTEIN METABOLISM

Day of Disease	Volume c.c.	Specific Gravity	Reaction	Albumin	Indican	Total Nitrogen Gm	Albumin Nitrogen	Amid Nitrogen Gm	Per Cent T N	Ammonia Nitrogen Gm	Urea Nitrogen Gm	Per Cent T N	Creatinin Nitrogen Gm	Per Cent T N	Creatinin Nitrogen Gm	Per Cent T N	
2	1440	1013	†	+++	++++	12.21	0.55	10.15	87.1	0.83	7.1	9.32	80.0	0.53	4.6	0.03	0.3
3	1220	1016	†	+++	++++	14.39	0.23	12.26	86.5	1.11	7.8	11.15	78.7	0.51	3.6	0.05	0.4
4	905	1015	†	+++	++++	12.32	0.13	10.88	89.3	0.82	6.7	10.06	82.6	0.36	2.9	0.10	0.8
5	1075	1017	†	+++	++++	15.43	0.61	13.43	90.7	1.11	7.5	12.32	83.2	0.40	2.7	0.10	0.7
6	910	1017	†	0	++++	15.59		12.83	82.3	0.91	5.8	11.92	76.5	0.35	2.2	0.08	0.5
7	820	1020	†	+	++++	16.37		13.19	80.6	0.94	5.7	12.25	74.9	0.37	2.3	0.16	1.6
8	450	1027	†	+	++++	9.71		8.44	86.9	0.45	4.6	7.99	82.3	0.24	2.5	0.14	1.8
9	450	1026	†	0	++++	10.24		9.02	88.1	0.36	3.5	8.66	84.6	0.22	2.1	0.10	1.6
10	600	1025	†	0	+++	12.65		11.66	92.3	0.61	4.8	11.05	87.4	0.28	2.2	0.19	1.5
11	No urine received																
12	1090	1016	‡	0	++	Urine decomposed											
13	840	1020	†	0	++++	Urine decomposed											
14	815	1025	†	0	+++	Urine decomposed											
15	820	1028	‡	0	+++	11.40		10.38	91.0	0.44	3.9	9.94	87.1	0.24	2.1	0.00	0.0
16	1100	1022	‡	0	++	11.78		11.31	96.0	0.32	2.7	10.99	93.3	0.19	1.6	0.00	0.0
17	940	1023	‡	0	++	11.02		10.30	93.5	2.29	20.8	8.01	72.7	0.26	2.4	0.00	0.0

examination was the amount of nitrogen excreted excessive We apparently have here an indication of two types of toxic condition, the one leading within the cell to a breaking down of protein and accompanied by a large amount of nitrogen in the urine, the other is shown by the irritative effect on the kidneys As will be seen, in some of the most toxic cases which we have examined—cases which are recognized clinically as most severe—not only is the nitrogen output extremely high but an intense nephritis is set up, as is shown by the large amount of albumin excreted in the urine

With regard to the individual constituents of the urine, one notes the absolutely high uric-acid excretion during the period of highest temperature, the increase of creatinin after the critical fall in temperature, and during convalescence the disappearance of creatin from the urine. In this case, as in Cases 1 and 13, one observes the sudden change in the composition of the rest nitrogen, as indicated by the change in the ratio of undetermined nitrogen to neutral sulphur. On the days of lower

## CASE 9, SEVERE PNEUMONIA

No.	Per Cent T N	Rest Nitrogen	Gm	Per Cent T N	Total Sulphur	Gm	T S	T N	Total Sulphate	Sulphur	Gm	Per Cent T S	Alkali Sulphate	Sulphur	Gm	Per Cent T S	Ethereal Sulphate	Sulphur	Gm	Per Cent T S	Neutral Sulphur	Gm	Per Cent T S	Rest Nitrogen	Gm	Phosphorus	Chlorin	Gm	Pulse	Temp ° Fahr			
1	27	0.63	5.3	0.92	7.5	0.61	66.3	0.53	57.6	0.08	8.7	0.31	33.7	49.3	0.11	2.34	140-112	104.8-104.0															
8	19	1.06	7.6	1.15	8.0	0.78	67.8	0.71	61.7	0.07	6.1	0.37	32.2	35.0	0.51	1.24	130-102	104.8-102.2															
12	18	0.64	5.2	0.86	7.0	0.62	72.1	0.58	67.4	0.04	4.7	0.24	27.9	37.5	0.15	0.65	120-100	105.0-101.8															
'8	19	0.61	4.1	0.97	6.3	0.74	76.3	0.69	71.1	0.05	5.2	0.23	23.7	37.6	0.52	0.58	120-92	102.4-100.6															
25	20	2.05	13.0	0.84	5.4	0.69	82.1	0.64	76.2	0.05	5.9	0.15	17.9	7.3	0.55	0.33	100-80	99.2-98.4															
14	21	2.31	14.0	0.92	5.6	0.76	82.6	0.72	78.2	0.04	4.4	0.16	17.4	6.9	0.85	0.25	90-74	99.2-98.0															
12	12	0.77	8.0	0.54	5.6	0.46	85.2	0.42	77.8	0.04	7.4	0.08	14.8	10.4	0.77	0.14	74-64	98.0-98.0															
10	10	0.80	7.8	0.52	5.1	0.44	84.6	0.41	78.8	0.03	5.8	0.08	15.4	10.0	0.62	0.17	60-60	99.0-98.0															
04	0.4	0.48	3.7	0.66	5.2	0.56	84.8	0.53	80.3	0.03	4.5	0.10	15.2	20.8	0.82	0.97	66-66	98.0-															
13	11	0.65	5.8	0.84	7.4	0.76	90.5	0.72	85.7	0.04	4.8	0.08	9.5	12.3	1.01	3.59	74-	98.0-															
14	0.3	0.24	2.1	0.89	7.6	0.83	93.3	0.77	86.6	0.06	6.7	0.06	6.7	25.0	0.87	4.16	74-	98.0-															
12	11	0.34	3.0	0.87	7.9	0.80	92.0	0.75	86.2	0.06	5.8	0.07	8.0	20.6	1.03	5.13	100-	97.6-															

nitrogen excretion the ratio of neutral sulphur to rest nitrogen suddenly falls to 7.3 and 6.9, as against preceding ratios of 49.3 to 37.5.

The retention of phosphorus during the period of high temperatures, while not striking, is distinct and as the case proceeds to convalescence there is a steady rise in the excretion of these substances.

CASE 10.—The patient, P. L., male alcoholic with left lower lobe pneumonia and influenza, was admitted on the third day of disease January 10 in a serious condition, severely ill. On January 11, the patient was severely sick but slightly easier and more comfortable due to greater ease of breathing out of doors. On the 12th, condition same during the day, but at night the patient developed sud-

## PROTEIN METABOLISM IN PNEUMONIA

den delirium of alcoholic type On the 13th, the general condition same except that delirium had diminished, 540 c.c. of semi-purulent fluid were drawn from the left chest On the 14th, respirations were easier, but general conditions and delirium about the same, on the 15th, general conditions slightly but distinctly better, on the 16th, the patient was slightly better On January 17, his general condition was much improved, mental condition normal, January 18, improvement continued, January 19, patient still improved On January 20, general condition was not quite so good, signs of fluid had returned, on the 21st, the patient was not quite so well On the 22d, conditions were good but not improving, 450

TABLE 10.—PROTEIN METABOLISM

Day of Disease	Volume c.c.	Specific Gravity	Reaction	Albumin	Indican	Total Nitrogen	Albumin Nitrogen	Amid Nitrogen	Per Cent T N	Urea Nitrogen	Per Cent T N	Creatinin Nitrogen	Per Cent T N	Creatinin Nitrogen	Per Cent T N	Uric Acid Nitrogen
2	300	1023	‡	+	+++	6.02	5.05	83.9	0.59	9.8	4.46	74.1	0.23	3.8	0.01	—
3	350	1023	†	+++	+++	5.72	0.88	4.01	82.8	0.44	9.0	3.57	73.8	0.25	5.2	0.01
4	785	1020	†	+	+	11.23	9.04	80.5	1.59	14.2	7.45	66.3	0.41	3.7	0.02	—
5	715	1020	‡	+	0	8.04	5.91	73.5	1.24	15.4	4.67	58.1	0.42	5.2	0.07	0.09
6	380	1018	†	+	0	5.05	4.03	79.9	0.53	10.5	3.50	69.4	0.23	4.6	0.11	2.1
7	912	1012	†	+	0	7.95	6.44	81.0	0.94	11.8	5.50	69.2	0.38	4.8	0.17	2.1
9	670	1020	†	+	0	9.66	7.88	81.6	0.94	9.8	6.94	71.8	0.43	4.4	0.25	2.6
10	470	1021	†	+	0	7.83	6.13	83.7	1.09	15.0	5.04	68.7	0.27	3.7	0.14	1.0
11	800	1015	†	+	+	8.94	7.26	81.2	0.56	6.3	6.70	74.9	0.35	4.0	0.16	1.8
12	618	1017	†	+	+	7.73	5.46	70.7	0.64	8.2	4.82	62.5	0.33	4.3	0.17	2.2
13	905	1012	‡	0	0	7.79	6.07	77.9	1.84	23.6	4.23	54.3	0.36	4.6	0.18	2.3
14	850	1014	‡	0	0	8.34	6.38	76.5	5.58	66.9	0.80	9.6	0.37	4.4	0.10	1.0
15	670	1013	‡	0	0	5.89	4.55	77.2	1.54	26.3	3.01	50.9	0.28	4.8	0.03	0.6
16	820	1012	‡	0	0	6.09	4.82	79.1	2.71	44.5	2.11	34.6	0.33	5.4	0.06	1.0

c.c. of bloody fluid drawn from the left chest January 23, 24 and 25, conditions remained stationary Operation was decided on the 25th, and on the 26th 200 c.c. of brownish, bloody pus were drained from chest Patient's condition was good, January 27, it was improved, and from then on the patient made a slow but good recovery

This case, one which must be regarded as a severe type of inflammation of the lung, is complicated by an empyema The examination of the case is incomplete, for the reason that estimation of nitrogen content of the pyemic fluid was not made During the examination the patient was tapped twice, and altogether 840 c.c. of pus removed

The nitrogen is distributed more on the lines of a non-nitrogenous high carbohydrate diet the ammonia ratio high, urea ratio low, and undetermined nitrogen high

Apparently the condition was of such a type as to allow the nitrogen catabolism to be amenable to protection with carbohydrate.

It is also interesting to note that the ratio of neutral sulphur to undetermined nitrogen is very close to what Folin found in normal cases on a non-nitrogenous diet. For example, a recalculation of the lowest nitrogen output in Tables 7 and 5 of Folin's article gives a ratio of neutral sulphur to rest nitrogen of 20.0 and 15.4.

#### CASE 10, SEVERE PNEUMONIA

Day	Rest Nitrogen per Cent N	Total Sulphur Gm	T S T N		Total Sulphate Sulphur		Per Cent S		Alkali Sulphate Sulphur		Per Cent S		Iodoethanol Sul- phate Sulphur		Per Cent S		Neutral Sulphur Gm		Per Cent S		Chlorin Gm		Phosphorus		Neutral S Rest Nitrogen		Pulse	Temp ° Fahr	
			T	S	T	N	Gm	Gm	Gm	Gm	Gm	Gm	Gm	Gm	Gm	Gm	Gm	Gm	Gm	Gm	Gm	Gm	Gm	Gm	Gm	Gm	Gm		
72	12.0	0.33	5.5	0.20	60.6	0.17	51.5	0.03	9.1	0.13	39.4	0.69	0.08	18.0	136-120	103	0-101.8												
41	8.5	0.38	6.6	0.21	55.3	0.17	44.7	0.04	10.6	0.17	44.7	0.49	0.18	41.5	126-122	102	2-100.0												
56	13.8	0.82	7.3	0.55	67.1	0.49	59.8	0.06	7.3	0.27	32.9	1.43	1.28	17.3	126-118	101	6-101.0												
60	19.9	0.56	7.0	0.31	55.4	0.27	48.2	0.04	7.2	0.25	44.6	1.43	0.21	15.6	126-120	102	2-101.2												
52	10.2	0.35	6.9	0.24	68.6	0.22	62.8	0.02	5.8	0.11	31.4	0.44	0.37	21.1	120-112	102	8-100.8												
64	8.1	0.63	7.9	0.43	68.3	0.39	61.9	0.04	6.4	0.20	31.7	0.72	3.2	120-110	102	0-100.4													
96	10.0	1.18	12.2	0.96	81.3	0.92	78.0	0.04	3.3	0.22	18.7	0.65	0.23	22.9	108-100	101	2-100.0												
68	9.2	0.94	12.8	0.77	81.9	0.73	77.7	0.04	4.2	0.17	18.1	0.40	0.42	25.0	120-96	101	0-110.4												
87	10.8	0.67	7.5	0.46	68.7	0.40	59.7	0.06	9.0	0.21	31.3	0.54	0.47	21.6	120-102	102	2-99.8												
160	20.6	0.51	6.6	0.31	60.8	0.26	51.0	0.05	9.2	0.20	39.2	0.38	0.72	12.5	116-102	101	6-100.6												
107	13.8	0.51	6.5	0.34	66.7	0.27	52.9	0.07	13.8	0.17	33.3	0.44	0.56	15.8	116-100	101	8-100.4												
11	17.1	0.56	6.7	0.35	62.5	0.30	53.6	0.05	8.9	0.21	47.5	0.62	0.51	14.8	116-100	101	4-99.2												
38	16.5	0.40	6.8	0.27	67.5	0.24	60.0	0.03	7.5	0.13	32.5	0.40	0.40	13.2	110-92	101	0-99.8												
57	10.7	0.39	6.4	0.23	59.0	0.19	48.7	0.04	10.3	0.16	41.0	0.69	0.47	23.6	110-100	101	0-99.8												

With the exception of two days of distinctly high ratio, namely, 41.5, 31.2 and 25.0, the values found in the present case are practically within the normal figures given there, in other words, the rest nitrogen in this case appears to have a composition, as far as its content in sulphur goes, very close to what has been observed in the normal.

CASE 11.—The patient F—d, male, aged 27, non alcoholic, came to the hospital May 15, on the eighth day of disease, having been untreated, severely sick on admission. Temperature was 104, pulse 168, respiration 48. Next day, the 16th, the patient was still severely sick and delirious, on the 17th, he was distinctly better and defervescence began and was completed on the morning of the 18th, on which day he was greatly improved. On the 19th and 20th, he was comfortable and convalescent, on the 21st, pleuritic pain was marked, on the 22d, patient was comfortable, on the 23d, he sat up in bed. On the 24th, he was up in ward and on the 25th, discharged.

The urines in this case were examined during the period of the crisis, which had apparently begun before the examination. The maximum rise in nitrogen took place on the fourth day, when the temperature had practically reached normal. There was a slight increase also on the seventh day, accompanied, however, by a distinct but fleeting rise in the temperature. From then on the patient passed into a condition of practical nitrogen equilibrium.

The creatinin nitrogen was low. On the first day of the examination a notable quantity of creatin nitrogen was excreted, 0.31 gm., but this rapidly fell, and while throughout the examination small quantities were constantly present, the amounts excreted daily were small.

TABLE 11—PROTEIN METABOLISM

Day of Disease	Volume c.c.	Specific Gravity	Reaction	Albumin	Indican		Total Nitrogen	Amid Nitrogen	Per Cent T N	Ammonia Nitrogen	Per Cent T N	Urea Nitrogen	Per Cent T N	Creatinin Nitrogen	Per Cent T N	Creatinin Nitrogen	Per Cent T N	Urine Acid Nitrogen	Per Cent T N
							Gm	Gm	Gm	Gm	Gm	Gm	Gm	Gm	Gm	Gm	Gm	Gm	Gm
2	845	1026	†	+	++		18.72	16.63	88.8	0.89	4.7	15.74	84.1	0.41	2.2	0.31	1.7	0.27	
3	720	1027	†	+	++		19.20	17.54	91.4	1.02	5.3	16.52	86.1	0.33	1.7	0.07	0.4	0.30	
4	800	1028	†	0	++++		22.51	20.82	92.5	1.48	6.6	19.34	85.9	0.38	1.7	0.11	0.5	0.34	
5	620	1029	†	0	++		16.39	15.21	92.8	0.86	5.3	14.35	87.5	0.30	1.9	0.09	0.6	0.24	
6	730	1028	†	0	+++		16.85	15.59	92.5	1.39	8.3	14.20	84.2	0.35	2.1	0.09	0.6	0	
7	840	1027	‡	0	+		17.87	16.07	89.9	1.53	8.6	14.54	81.3	0.43	2.5	0.08	0.4	0	
8	630	1029	†	0	++		13.33	11.94	89.5	0.74	5.5	11.20	84.0	0.32	2.4	0.11	0.8	0.10	
9	1040	1025	†	0			16.56	15.04	90.8	0.77	4.6	14.27	86.2	0.42	2.5	0.09	0.6	0.21	
10	960	1020	†	0			13.67	12.50	91.4	0.75	5.5	11.75	85.9	0.36	2.7	0.07	0.5	0.17	

While the chlorin disappeared entirely, on one day of the examination, the phosphorus increased steadily, reaching its maximum on the last day of the disease. The chlorin had, however, become maximal in amount the day previous.

CASE 12.—The patient, H. C., male, aged 27, until one year ago was very alcohol, had syphilis seven years ago, was admitted on sixth day of disease with left upper lobe involved and with a small area in the upper portion of the right lower lobe and also area in the right upper lobe. He seemed dull and sicker than his symptoms indicated. On the night of the 21st he was restless and uncomfortable, on the 22d, nauseated and vomited his food, was restless, dull, and seemed severely sick. New area of consolidation appeared in the right upper lobe. On the 23d, the patient was more comfortable and general condition improved, began to defervesce. On the 24th, defervescence was complete and

general condition much improved. On the 25th, consolidation in left lower lobe was resolving, patient comfortable, and general condition excellent. On the 26th, patient was convalescent, and continued so uninterruptedly.

This case was one characterized clinically as very severely toxic in type, and a review of the results given by the examination of the urine substantiates that view.

The urine was examined from the time of entrance of the patient to the hospital. The defervescence extended over four days. On these days the nitrogen excretion varied between 31.2 and 27.2 gm. Even after a normal temperature was reached the nitrogen elimination still continued excessively high, and for five days (in one of which the urine was lost)

CASE 11. SEVERE PNEUMONIA

		Per Cent	T N																	
10	5.9	1.36	7.3	1.16	85.3	1.11	81.6	0.05	3.7	0.20	14.7	18.2	0.66	0.30	164-128	103.8-102.8				
96	5.0	1.27	6.6	1.11	87.4	1.05	82.7	0.06	4.7	0.16	12.6	16.7	0.66	0.04	112-104	103.0-101.2				
\$6	3.8	1.44	6.9	1.32	91.7	1.24	86.2	0.08	5.5	0.12	8.3	14.0	0.87	0.00	100-88	100.4-98.8				
55	1.2	1.06	6.5	0.94	88.7	0.88	83.0	0.06	5.7	0.12	11.3	21.8	0.73	0.15	96-84	99.6-98.4				
					Not determined											92-76	99.2-98.6			
					Not determined											96-72	101.2-98.8			
77	7.0	0.81	6.3	0.74	88.1	0.71	84.5	0.03	3.6	0.10	11.9	13.0	0.98	1.89	86-72	99.6-98.4				
100	1.8	1.16	7.0	1.01	87.1	0.94	81.0	0.07	6.1	0.15	12.9	18.7	1.10	3.68	88-76	99.2-98.4				
77	1.1	1.00	7.3	0.86	86.0	0.81	81.0	0.05	5.0	0.14	14.0	24.5	1.12	2.07	88-72	99.2-98.4				

the nitrogen excreted was from 22.7 to 18.3 gm. Not only is the total nitrogen output high, but during the febrile period the ratio of amid nitrogen to total nitrogen is much below the normal for this amount of nitrogen. As the ammonia ratio is low—quite within the supposedly normal limits for this amount of nitrogen—the rest nitrogen rises to most unusual absolute values.

On the first day of the examination unknown substances containing 5.82 gm of nitrogen were excreted. In only one (Case 13) of the other cases have we found amounts in any way approaching this. For seven days a very high test nitrogen was exhibited, falling at times to 1.01. On the fifteenth day of the disease the composition of the urine changed com-

pletely from that of the previous day. The patient went instantly into practical nitrogen balance and produced a urine normal in composition. The creatinin output on the first days of the examination was well above what has been found in the cases so far discussed falling on the ninth day to a value to be found in most normal cases of this disease.

The creatin output is extremely high, on some of the days approaching very closely to creatinin output itself. It is noticeable also that the final fall in creatin precedes the day of low nitrogen excretion. Throughout the febrile period of the case the uric-acid nitrogen is also extremely high. Its fall precedes that of the total nitrogen.

TABLE 12.—PROTEIN METABOLISM

Day of Disease	Volume c.c.	Specific Gravity	Reaction	Albumin	Indican	Gm	Total Nitrogen	Albumin Nitrogen	Amid Nitrogen	Per Cent T N		Ammonia Nitrogen	Gm	Urea Nitrogen	Per Cent T N		Creatinin Nitrogen	Gm	Per Cent T N		Creatin Nitrogen	Gm	Uric Acid Nitrogen	Gm	
										T	N				T	N			T	N					
6	1420	1027	†	+++	+	31.2	1.00	24.00	76.9	1.16	3.7	22.84	73.2	0.70	2.2	0.44	1.4	0.24							
7	1320	1024	†	+	0	30.54		26.65	87.3	1.24	4.1	25.41	83.2	0.61	2.0	0.55	1.8	0.45							
8	1360	1022	†	+	0	31.22		27.52	88.1	1.37	4.4	26.15	83.7	0.60	1.9	0.49	1.6	0.44							
9	1220	1023	†	+	0	27.20		24.55	90.3	1.05	3.9	23.55	86.4	0.42	1.6	0.30	1.1	0.3							
10	980	1026	†	+	+	22.72		20.02	90.1	0.51	2.2	19.51	87.9	0.46	2.0	0.17	0.7	0.1							
11	1000	1029	†	+	0	22.53		20.48	90.9	0.93	4.1	19.55	86.8	0.41	1.8	0.20	0.9	0.1							
Urine lost																									
13	1020	1026	†	+	0	18.32		16.69	90.1	1.04	5.7	15.65	85.4	0.42	2.3	0.11	0.6	0.1							
14	1012	1027	†	0	0	19.24		17.23	89.5	1.21	6.3	16.02	83.2	0.50	2.6	0.03	0.3	0.1							
15	385	1029	†	+	0	8.09		7.41	91.5	0.50	6.1	6.91	85.4	0.18	2.2	0.04	0.5	0.0							
16	600	1025	†	0	0	9.78		9.00	92.0	0.72	7.4	8.28	84.6	0.25	2.6	0.03	0.3	0.0							

With the exception of the first two days, one notes that the ratios obtained for the total sulphate sulphur to total sulphur are very high, so that as a consequence the neutral sulphur is comparatively low, especially when one compares it with the excessive amount of rest nitrogen excreted. One can only believe, therefore, that in this case in the group of unknown substances excreted as rest nitrogen there is a relatively great preponderance of those which contain a very low proportion of sulphur.

#### FATAL CASES

The following cases terminated fatally, but do not comprise the complete results of all examined. In some of the instances the delirium was

so great that we were unable to collect twenty-four-hour specimens of urine. In some cases the patients entered the hospital in an alcoholic delirium and no satisfactory history or examination could be made.

CASE 13.—The patient, J. W., male, age unknown, alcoholic, with delirium tremens, was admitted with right lower lobe and right upper lobe involved. No history was obtainable. On admission, May 2, patient was evidently seriously ill and delirious, on May 3, general condition was fair, there were paroxysms of marked dyspnea, the patient was still evidently seriously ill. On May 4, condition was about same, May 5, patient's general condition not as good, pulse was worse. On May 6, patient was still delirious, condition fair, May 7, about same, May 8, further extension in right upper lobe, delirium more pronounced, patient evidently worse. On May 9, temperature was lower, but pulse and

## CASE 12, SEVERE PNEUMONIA

Rect Nitrogen Gm	Per Cent N	Total Sulphur Gm	T S T N	Total Sulphate Sulphur Gm	Per Cent T S	Alkaline Sulphate Sulphur Gm	Per Cent T S	Ethereal Sulphate Sulphur Gm	Per Cent T S	Neutral Sulphur Gm	Per Cent T S	Rest Neut N Gm	Chlorin	Phosphorus Gm	Pulse	Temp ° Fahr
5.82	18.7	2.40	7.7	1.91	79.6	1.88	78.3	0.03	1.3	0.49	20.4	8.4	0.35	2.00	120-108	104.2-102.8
2.28	7.4	2.02	6.4	1.62	80.2	1.56	77.2	0.06	3.0	0.40	19.8	17.5	0.32	1.46	120-108	103.4-101.5
2.12	6.8	2.03	6.4	1.66	81.8	1.61	79.3	0.05	2.5	0.37	18.2	17.4	0.49	1.40	104.92	102.0-101.5
1.63	5.9	1.71	6.9	1.53	89.5	1.48	86.6	0.05	2.9	0.18	10.5	11.0	0.88	1.74	88.84	99.5-99.0
1.71	5.8	1.56	6.8	1.37	87.8	1.30	83.3	0.07	4.5	0.19	12.2	11.1	1.07	1.61	92.76	98.6-98.0
1.26	5.6	1.58	7.0	1.39	87.9	1.32	84.1	0.07	3.8	0.19	12.1	15.1	3.40	1.33	84.80	99.5-98.4
1																
1.01	5.5	1.25	6.8	1.19	99.5.2	1.13	90.4	0.06	4.8	0.06	4.8	5.9	7.09	1.14	92.68	98.6-98.4
1.20	6.7	1.35	7.0	1.20	88.9	1.15	85.2	0.05	3.7	0.15	11.1	11.6	7.39	1.28	84.76	99.8-98.6
0.30	4.9	0.57	7.0	0.47	82.5	0.43	75.4	0.04	7.1	0.10	17.5	25.6	2.23		84.84	99.4-98.6
0.42	4.3	0.71	7.2	0.62	87.3	0.57	80.3	0.05	7.0	0.09	12.7	21.4	5.22	0.62	92.80	99.0-98.2

respirations much worse. On the 10th, most of the day patient seemed a little better, but in late afternoon grew worse. Entire right lower lobe was consolidated, patient evidently worse. On the 13th, patient continued delirious, and pulse was worse in character and faster in rate. Condition was very bad. On the 14th, patient died.

This typical case we were able to examine over an extensive period, during which the temperature never fell to normal. It is like the preceding in showing an amount of undetermined nitrogen on the first day of the examination above that of any so far recorded in the literature.

Creatinin was excreted in an unusually high amount, on the first day of the examination. The patient was a small man, weighing probably not more than 70 kilos. In this instance the creatinin coefficient was

undoubtedly at least 11.0, a value which has only so far been approached in typhoid fever,<sup>28</sup> and by Hoogenhuyze and Verploegh<sup>29</sup> in muscular effort in which the metabolism is at a very high level.

What is quite remarkable is the absence of creatin in these urines until the last of the examination, when the creatin nitrogen steadily rises. During the time no creatin was found a large amount of muscle tissue was probably catabolized. This unusual state of affairs would tend to show

TABLE 13—PROTEIN METABOLIS

Day of Disease	Volume cc	Specific Gravity	Reaction	Albumin	Indian	Gm	Total Nitrogen	Albumin Nitrogen	Gm	Ammonia Nitrogen	Gm	Urea Nitrogen	Gm	Creatinin Nitrogen	Gm	Per Cent T N	Ur. Acids			
1	1716	1017	-	+++	++	27.85	0.53	19.65	72.0	1.63	6.0	18.02	66.0	0.79	2.9	0.00	0.0	0.0	0.0	0
2	1000	1019	+	++	++	Urine decomposed														
3	1260	1017	+	++	++	21.62		19.47	90.1	1.40	6.5	18.07	83.6	0.58	2.7	0.00	0.0	0.0	0	
4	825	1018	-	+++	++	15.25	0.10	14.15	93.4	0.45	3.0	13.70	90.4	0.35	2.3	0.00	0.0	0.0	0	
5	1360	1019	-	+++	++	23.88	0.28	21.50	91.2	0.61	2.6	20.89	88.6	0.64	2.7	0.00	0.0	0.0	0	
6	1365	1020	-	++	++	26.25		24.50	93.4	1.43	5.5	23.07	87.9	0.57	2.2	0.00	0.0	0.0	0	
7	1360	1019	-	+	+++	28.90		27.26	94.4	0.54	1.9	26.72	92.5	0.47	1.6	0.09	0.3			
8	1040	1020	-	+	++++	24.17		22.70	94.0	1.90	7.8	20.80	86.2	0.38	1.5	0.04	0.2			
9	1160	1024	-	+	+++	25.46		23.76	93.3	0.41	1.6	23.35	91.7	0.56	2.2	0.06	0.2			
10	1220	1023	-	0	++++	26.47		24.50	92.5	0.30	1.1	24.20	91.4	0.51	1.9	0.08	0.3			
11	780	1025	-	0	++++	12.75		11.22	88.0	0.30	2.3	10.92	85.7	0.40	3.1	0.13	1.0			
12	940	1022	-	0	++++	14.23		12.73	89.4	0.23	1.6	12.50	87.8	0.38	2.6	0.26	1.8			
13	1021	-	+					83.5		3.8		79.7		5.1		2.7				

that the breaking down of body protein alone, such as occurs in starvation, is not the only factor essential to the appearance of creatin in the urine. It is notable also that the amount of creatin steadily rises until death occurs—the amount excreted on the day before death is highest. If one may use the relative figures which were obtained for an incomplete specimen of urine on the last day, one may assume that both creatinin and creatin were higher on these days than on any preceding.

The total sulphur in this case merits some attention. In most of the other cases examined the ratio of total sulphur to total nitrogen varied between 6.0 and 7.5. In this case much higher ratios obtained, in one

28 Shiffner, P. A. Am Jour Physiol, 1908, xxviii, 16

29 Hoogenhuyze and Verploegh Ztschr physiol Chem, 1905, xvi, 415

day being 9.8, except on the first day when 9.6 per cent of total nitrogen was excreted as total sulphur the highest values were obtained at the end. One might be led to infer that this catabolism of a protein high in sulphur toward the end of the disease was significant, for it has been seen in other conditions—notably delayed chloroform poisoning in animals—but such is not altogether the case, for in other lethal cases of pneumonia which we have examined the ratios are low toward the end.

## CASE 13, FATAL PNEUMONIA

In st Nitrogen Gm	Per Cent N	Total Sulphur Gm	T S T N			Total Sulphate Sulphur Gm	Alkali Sulphate Sulphur Gm	Per Cent TS	Per Cent TS	Ethereal Sul- phate Sulphur Gm	Per Cent TS	Neutral Sulphur Gm	Per Cent TS	Neutral S Nitrogen Gm	Rest Phosphorus Gm	Chlorin Gm	Pulse	Temp ° Fahr	
			T	S	T N														
6.57	24.0	2.68	9.6	2.24	83.6	2.19	87.6	0.05	2.0	0.44	16.4	6.7	1.46	0.00	128	110	104.0	102.8	
7.143	6.5	1.93	8.9	1.53	79.2	1.48	76.5	0.05	2.7	0.40	20.8	28.0	0.22	0.15	132	88	105.2	103.8	
7.058	3.8	1.07	7.0	0.86	80.3	0.82	76.6	0.04	3.7	0.21	19.7	36.2	0.35	0.15	152	100	105.4	102.6	
9.122	5.1	1.91	8.0	1.58	82.7	1.51	79.1	0.07	3.6	0.33	17.3	27.0	0.94	0.08	136	118	104.8	104.0	
8.101	3.6	1.81	7.0	1.63	88.6	1.56	84.8	0.07	3.8	0.21	11.4	21.0	0.82	0.08	140	110	103.8	102.0	
2.101	3.5	1.75	6.1	1.60	91.4	1.50	85.7	0.10	5.7	0.15	8.6	15.0	1.22	0.24	140	128	104.8	102.6	
7.081	3.5	1.31	5.5	1.17	89.3	1.09	83.2	0.08	6.1	0.14	10.7	16.7	0.48	0.19	132	120	102.4	100.2	
7.095	3.8	1.54	6.0	1.43	92.9	1.35	87.7	0.08	5.2	0.11	7.1	11.6	1.05	0.28	144	120	105.0	100.8	
7.121	4.8	1.62	6.1	1.48	91.4	1.40	86.4	0.08	5.0	0.14	8.6	11.3	1.32	0.00	144	112	104.4	100.8	
7.092	7.3	1.26	9.8	1.16	92.1	1.07	84.9	0.09	7.2	0.10	7.9	10.9	1.19	0.05	140	120	103.6	100.2	
7.078	5.6	1.31	9.2	1.18	90.1	1.04	79.4	0.14	10.7	0.13	9.9	16.7	0.99	0.11	140	120	104.0	101.0	
					93.4		87.6			5.8		6.6					132-120	104.2	103.2

In this, as in Case 12, the ratios for the various components of the sulphur partition are high, denoting a very efficient capacity for oxidizing the large amount of sulphur excreted.

CASE 14—The patient, J. W., was admitted with right lower lobe only involved, no history obtainable on admission, and on March 1, the patient's general condition was good, he seemed severely sick. On the 2d, the left lower lobe became involved and patient's condition became more serious. On the 3d, he was very ill, though his general condition was not alarming. On the 4th, his condition was not better. On the 5th, patient was worse, became delirious. On the 5th, the right lower lobe was resolving, but general condition was very bad. On the 7th, he died.

This case shows a somewhat different course in the nitrogen metabolism, as the amount of nitrogen excreted rose toward the end. In this case

we have the pneumonic condition attended with a nephritis so intense that on the day on which the patient died 8.33 gm of albumin nitrogen, equivalent to about 52.1 gm of albumin, were excreted. The amount of albumin excreted varied between wide limits and was not progressive. The ammonia nitrogen in this case was high. On the last day of the illness 48.5 per cent of the total nitrogen, excluding albumin nitrogen, was excreted in this form. It is possible that the urine on this date was decomposed, but it is doubtful. It is worth while noting that in two cases the day of death was accompanied by an alkaline urine in which a large part of the nitrogen was excreted in the form of ammonia.

The creatinin nitrogen in this case exceeds on an average anything which has been found in any previous case, and on the day of death reaches a maximum. With the high output of creatinin we have a most

TABLE 14—PROTEIN METABOLISM

Day of Disease	Volume c.c.	Specific Gravity	Reaction	Albumin	Indican	Total Nitrogen	Albumin Nitrogen			Per Cent T N	Ammonia Nitrogen	Urea Nitrogen	Per Cent T N	Creatinin Nitrogen	Per Cent T N	Creatinin Nitrogen	Per Cent T N	Uricle Acid Nitrogen
							Gm	Gm	Gm									
3	975	1023	†	+++	0	16.48	2.83	11.78	86.3	1.14	8.4	10.64	77.9	0.74	5.4	0.00	0.0	0
4	1645	1019	†	++++	+	27.80	6.76	18.00	85.6	1.00	4.7	17.00	80.9	0.72	3.4	0.56	2.6	0
5	1720	1012	†	+++	0	19.10	1.44	15.12	85.6	1.74	9.8	13.38	75.8	0.60	3.4	0.43	2.5	0
6	1620	1013	†	+++	0	21.02	2.38	15.86	82.4	1.18	6.3	14.18	76.1	0.62	3.3	0.58	3.1	0
7	1640	1027	‡	++++	+	29.14	8.33	17.40	83.6	10.10	48.5	7.30	35.1	0.75	3.6	0.64	3.1	0

unusually high creatin elimination, suddenly appearing on the second day of the examination. Clinically the case might easily be compared with the preceding yet there is a marked difference in the metabolism of the two cases. In the one no creatin is found, in the other, creatin appears in the urine and reaches a level which is not found in any of the other cases examined.

The uricle acid nitrogen is high throughout, but does not call for any special comment, except to point out the unusual amount 0.43 gm, excreted on the terminal day.

The rest nitrogen, compared with what has been found in some of the other cases of severe toxic pneumonia, is both relatively and absolutely low.

A comparison of the neutral sulphur with the undetermined nitrogen shows the fluctuating character of the latter, with respect to sulphur

The ratios vary from 48.2 to as low as 8.4. No relationship with the severity of the condition nor with any of the important factors of the nitrogen partition can be made out.

#### SUMMARY

The nitrogen and sulphur metabolism in 19 cases of pneumonia of varying degrees of severity have been examined.

The cases of milder type show a smaller loss in nitrogen and sulphur than do those of a more severe grade. The daily loss in nitrogen on a diet adequate to protect a resting individual from nitrogen loss may be from 20 to 25 gm.

The relative desamidating capacity, as shown by the ratio of urea nitrogen to total nitrogen, is comparable to that of a normal subject.

#### CASE 14, FATAL PNEUMONIA

	Rest Nitrogen Gm	Per Cent T N Gm	Total Sulphur Gm	T S T N Gm	Total Sulphate Sulphur Gm	Per Cent T S Alkali Sulphate Sulphur Gm	Per Cent T S Ethereal Sul- phate Sulphur Gm	Per Cent T S Per Cent T S Neutral Sulphur Gm	Per Cent T S Chlorin Gm	Per Cent T S Phosphorus Gm	Neutral S Rest Nitrogen Gm	Pulse	Temp ° Fahr				
7	0.55	6.6	1.21	7.3	0.80	66.1	0.77	63.6	0.03	2.5	0.41	33.9	1.60	1.50	48.2	124-106	105.2-101.2
6	1.12	6.8	1.57	5.6	1.45	92.4	1.42	90.5	0.03	1.9	0.12	7.6	2.99	0.98	8.4	138-120	105.2-102.0
1	1.27	7.2	1.24	6.5	0.95	76.6	0.92	74.2	0.03	2.4	0.29	23.4	0.52	1.25	22.8	136-120	104.6-103.8
0	1.50	10.2	1.39	6.6	1.14	82.1	1.12	80.6	0.02	1.5	0.25	17.9	0.88	1.02	13.2	136-120	104.0-103.0
5	1.58	7.2	2.16	7.4	1.19	69.0	1.44	66.7	0.05	2.3	0.67	31.0	0.70		42.3	130-112	105.0-104.0

The capacity for the oxidation of the cystin group, as exhibited by the ratio of total sulphate sulphur to total sulphur, is quite as high, if not higher than normal.

During the period of hyperpyrexia excessive amounts of creatinin are eliminated. This is followed during convalescence by a subnormal excretion of creatinin. This is taken to indicate the endeavor on the part of the organism to repair the losses sustained during the height of the toxemia.

In the severe cases of pneumonia large amounts of creatin are also excreted. This is seen particularly during the time of greatest nitrogen loss. During convalescence the creatin disappears from the urine. In some of the lethal cases the amount of creatin excreted on the day terminating the illness is as high as the amount of creatinin excreted.

During hyperpyrexia, especially in cases severely toxic in type, unusually high amounts of undetermined nitrogen are excreted. In some cases over 5 gm of nitrogen derived from uninvestigated substances are found in the urine. This nitrogen is not derived from albumoses, as the search for these substances revealed quantities which in no way could account for the large amount of rest nitrogen.

The sulphur excretion runs more or less parallel with that of the nitrogen, but it appears in some of the cases that the catabolism of proteins rich in sulphur is not so marked as those in which the content of sulphur is small. On the other hand, cases progressing unfavorably seem to show an excessive destruction of proteins containing much sulphur. This is made out from the increased ratio of total sulphur to total nitrogen.

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## THE BACTERIOLOGY OF ACUTE INFECTIONS OF THE RESPIRATORY TRACT IN CHILDREN, WITH ESPECIAL REFERENCE TO INFLUENZA

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One of the most striking changes in the mortality figures of the last twenty-five years is in the increase in the deaths from acute respiratory diseases, especially bronchitis and pneumonia. This has affected all ages, infants and young children, as well as adults. As respects infants, the mortality from respiratory diseases in New York touched the high point in 1902, since which time it has fallen but little. This increase is in striking contrast with the steady decline in acute infections of the gastrointestinal tract, these having fallen almost as steadily as those of the respiratory tract have risen. Thus twenty-five years ago the deaths under one year from acute intestinal diseases numbered 3,300, the same year those of bronchitis and pneumonia numbered only 1,350. In 1902 the deaths from acute respiratory diseases were greater by nearly one hundred than those from acute intestinal diseases the following year. Nowhere has this increase been more marked than in institutions, especially in those for infants and young children. Nothing in a hospital service is more discouraging than the development of such complications as acute nasopharyngitis and otitis, laryngitis, bronchitis and bronchopneumonia in children admitted for other diseases or for surgical operations. In fact, these infections have come to be almost as serious as the development of scarlet fever, measles or diphtheria, and often more difficult to control because the source of infection and manner of spreading are less obvious.

I had shared the opinion that for the increase in acute respiratory diseases influenza especially was largely responsible. In order to determine what part this actually played in our respiratory infections, systematic observations were begun in the Babies' Hospital in December of 1908 and continued through the following winter and spring, with some observations during the summer months for control.

In working out this problem I have been fortunate in having the assistance of our pathologist, Dr. Martha Wollstein who for several years

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\* Read at a meeting of the American Pediatric Society at Lenox, Mass., May 27, 1909.

has devoted much time to the study of the bacillus of influenza and allied organisms. This fact is a sufficient guarantee of the accuracy of the bacteriological part of this report. I desire also to express my obligations to Dr. Josephine Hemenway for valuable assistance in carrying out this investigation.

Realizing the vagueness with which the term "influenza" is used, we endeavored to discover how much real influenza existed which could be demonstrated by cultures, accepting nothing as of diagnostic value except the presence of Pfeiffer's bacillus.

#### CLINICAL OBSERVATIONS

We began by making cultures from all suspicious cases, i.e., those of patients with moderate or severe catarrhal inflammation of the upper and lower respiratory tract, and cases with high temperature without obvious explanation. Later this was extended to cover all respiratory catarrhs and all cases of pneumonia, empyema, otitis and all febrile cases of doubtful diagnosis, particularly those developing in the wards. At times cultures were taken from all the patients of certain wards, also from caretakers, nurses and physicians who were in contact with the children. Finally, cultures were made from the lungs and heart's blood at all autopsies whether influenza was suspected or not. It is scarcely necessary to state that the bacillus of influenza grows only on a medium containing hemoglobin, that of the rabbit's blood being found to be most convenient. Blood-agar plates were used for all our cultures.

It developed in the course of these observations that success depended in no small degree on the manner of taking the cultures. It was found that the bacilli were often difficult to obtain unless bronchial secretion could be secured. The cultures made, therefore, are to be regarded as sputum cultures rather than simple throat cultures. It was not always easy to secure sputum from the infants who composed most of our patients, but by following the plan pursued at the hospital for obtaining tuberculous sputum results were much improved. The child was made to cough by irritating its pharynx with a bit of gauze or cotton in the jaws of an artery clamp, and any secretion brought into view was secured on this swab. Not all children could be made to cough well, which explains some negative results in positive cases.

I have to report on observations made on thirty-six nurses, four physicians and about 250 children, repeated cultures having been taken from many of the persons. In addition to these observations on patients, cultures were made from the lungs and heart's blood in fifty-nine consecutive autopsies.

In the records of throat cultures no account has been taken of the *Micrococcus catarrhalis*, since this was found to be present in practically every child examined whether symptoms existed or not, and at first no account also of the staphylococcus.

The streptococcus was noted when present and also the pneumococcus. In the first few cases the latter was noted only when present in considerable numbers, but in the latter part of the season—including nearly three-fourths of the cases—the presence of the pneumococcus was noted in every instance in which it was observed.

The *B. influenzae* was discovered by cultures in eighty-five persons, of whom forty-two were suspected of having influenza and forty-three were not, fifteen of the latter being nurses or physicians who were in intimate contact with patients.

A suspicion of influenza in the forty-two cases rested on the following symptoms:

Obscure high temperature with few or no catarrhal symptoms	12
High and widely fluctuating temperature with or without pneumonia	7
Acute catarrhal symptoms with fever	3
Acute catarrhal symptoms with little or no fever	8
Severe catarrhal symptoms, protracted or recurring	9
Protracted bronchopneumonia	3

In the forty-three non-suspected cases in which the *Bacillus influenzae* was found the clinical condition of the subjects examined was as follows:

No symptoms (routine cultures), of which 15 were nurses	19
Moderate bronchitis, young infants exposed to influenza	7
Typical pneumonia with high temperature (one had crisis)	3
Empyema (one staphylococcus and one pneumococcus)	2
Nurses with slight cough and pharyngitis	2
Various others	10

In the beginning we made many mistakes, expecting to find the *B. influenzae* in cases of acute nasopharyngeal catarrh, but it was not found in a single one of five such cases developing in the wards, nor was the pneumococcus found.

Of 47 cases of acute bronchitis or pneumonia occurring in the winter or spring months the *B. influenzae* was found by cultures in 63 per cent, some of these patients were admitted with the disease and others developed it in the wards. I shall refer again to the clinical features of the influenza infections.

At this season of 113 persons giving negative influenza cultures, sixteen were suspected and ninety-seven were not forty-three of the latter being routine cultures taken from persons in no way ill. It is of some

interest that in two of the suspected cases giving negative cultures during life, the autopsy showed the *B. influenzae* in the lungs.

It is, I think, very significant that, while positive influenza cultures were frequently obtained through April and the early part of May, with the advent of warm weather this organism disappeared entirely from our patients. Cultures were made from twenty-seven persons in the latter part of May and through the month of June, and but once (this in the person of a nurse who had it many times before) was the *B. influenzae* found after May 20, though in some of these patients or nurses it had been regularly found during the previous weeks.

The association of the pneumococcus with both positive and negative influenza cultures is interesting. In the winter and spring observations of the patients giving positive influenza cultures, the pneumococcus was present in 48 per cent. Of the persons giving negative influenza cultures the pneumococcus was present in 27 per cent. Of the 74 cases of acute bronchitis and pneumonia seen at this season, 46 per cent showed the pneumococcus and 54 per cent did not, of those same 74 cases it will be recalled that 63 per cent had influenza and 37 did not. Although the *B. influenzae* disappeared with the advent of warm weather, pneumococcus infections persisted. Of twenty-seven June cultures it was present in ten, five of these were cases of pneumonia and five patients had no bronchial or pulmonary symptoms, though one developed pneumonia a few days later. Not only were pneumococcus infections seen in the respiratory tract, but several cases of pneumococcus ophthalmia occurred in the hospital during the summer. Our influenza, then, was limited to winter and spring, but pneumococcus infections persisted throughout the year.

Influenza and otitis are so often associated in the mind of the clinician that the bacteriological findings possess some interest. During the winter and spring season, cultures were made twenty-nine times after fresh paracentesis in cases of acute otitis. The staphylococcus was found twenty-five times, the pneumococcus, nine times, streptococcus, once, and the *B. influenzae* in not a single instance. Yet in throat cultures made from the same patients, fifteen of the twenty-nine showed the *B. influenzae* and three showed the pneumococcus. This result is to be taken in connection with the findings in the cases of acute nasopharyngitis, in which also no *B. influenzae* were found. These suggest that the relation of influenza to these complications resembles that of measles, in that it furnishes conditions in which the micro-organisms commonly present in these cavities become active and excite inflammation. In not one of five

cases of acute retropharyngeal abscess was the *B. influenzae* found either in the throat or the pus, these cases showed staphylococcus or streptococcus.

#### POST-MORTEM OBSERVATIONS

Cultures were made from the lungs and heart's blood in fifty-nine consecutive autopsies. Forty-seven were made in the winter and spring and twelve in the early summer. It is important to consider the two groups separately. In the winter and spring cases the *B. influenzae* was found in seventeen, twelve of these gave positive influenza cultures during life, two gave negative cultures, though influenza was suspected from the clinical symptoms, and in three no cultures were taken. Of the seventeen cases in which influenza was found, eleven were cases of acute bronchitis or acute bronchopneumonia, two were terminal pneumonia following malnutrition, three were pulmonary tuberculosis and one only was non-pulmonary. As in cultures made during life, the pneumococcus was found less frequently, i.e., in only thirteen of the forty-seven cases, six of these were acute bronchitis or bronchopneumonia, one a terminal pneumonia with malnutrition, two pulmonary tuberculosis, and four non-pulmonary cases. Considering only the sixteen cases of acute bronchitis and bronchopneumonia which came to autopsy, the *B. influenzae* was present in eleven and the pneumococcus in only six. In two cases of acute bronchopneumonia there was no growth from the lungs, in three cases neither the *B. influenzae* nor the pneumococcus was present but only the staphylococcus. Of special interest is one case in which a pure growth of the *B. influenzae* was obtained from the lungs, and another case in which a pure growth of this organism was obtained from a serofibrinous pleural exudate.

Of the twelve autopsies made in early summer, the *B. influenzae* was found in none, the pneumococcus in six, four of those obtained. In four staphylococci were present. The part played by the streptococcus in this series of pneumonia cases was not great. It was found in four cases only, never as the sole organism.

#### THE VALUE OF CULTURES FOR DIAGNOSIS

The question naturally arises how much value can be attached to cultures for the diagnosis of influenza. Some idea may be gained from our experience. Of fifty-eight persons suspected to be suffering from influenza the throat cultures were positive in forty-two and negative in sixteen; but in two of these negative cases the organism was obtained from the lungs at autopsy. On the other hand of 185 persons—patients or

inmates of the hospital—not suspected, the cultures were negative in 142 and positive in 43, 15 of the latter being nurses. There were only eleven persons from whom the first cultures were negative and later ones positive. Three of these gave two negative cultures before a positive one was obtained. The significance of these facts is lessened by the knowledge that the cultures were separated by some time, usually one to two weeks, so that it is perhaps quite as likely that a later infection occurred, as that the organism had been previously present but missed.

The proportion of positive throat cultures in suspected cases, 73 per cent, is, I think, sufficiently large to warrant one in attaching considerable importance to these results. Early in our observations we classed as "suspected," cases of acute nasopharyngitis, later experience proved this to be an error. Excluding these would raise our proportion of positive results to 80 per cent. While one cannot regard a single negative culture as having the same significance as a negative culture from a throat in suspected diphtheria, two or three negative cultures, if properly taken, can in most cases be depended on. Negative results in influenza are more reliable than are negative examinations for tubercle bacilli from sputum, since it is easier to demonstrate the *B. influenzae* by cultures than it is to discover the tubercle bacilli by staining smears.

#### THE SIGNIFICANCE OF THE BACTERIOLOGICAL FINDINGS

We have deferred until now a consideration of the important question which might very properly have been taken up at the outset, viz. What significance has the presence of the *B. influenzae* in the pharyngeal or bronchial secretions of persons suffering from acute febrile or catarrhal symptoms, or in apparently healthy persons in whom no such symptoms exist? When present with symptoms, is it fair to assume that it bears a causal relation to them? Is the *B. influenzae* in these cases the specific pathogenic organism, or only one of an associated group which together cause the familiar symptom-complex?

That the *B. influenzae* is pathogenic is, I think, now generally admitted, and I may say that so far as these observations go they show quite as much for the *B. influenzae* as they do for the pneumococcus. It is granted that in most of these cases we are dealing with mixed infections, but I would call especial attention to two cases which came to autopsy, one of which showed a pure culture of the *B. influenzae* in a serofibrinous pleural exudate, and in the other a pure growth of the same organism was obtained from a pneumonic lung. No blood-cultures were made during life. In no case in this series of 59 autopsies was the *B. influenzae*

obtained from cultures made at autopsy from the heart's blood<sup>1</sup>. No case of meningitis was seen in which it was the sole organism though a number of such cases have been reported to have occurred in Mount Sinai Hospital in New York and it has been found several times in the cerebrospinal fluid sent to the Rockefeller Institute, from cases suspected to be epidemic meningitis.

My own belief is that infection with the *B. influenzae* plays at the present time a very important part in acute inflammations of the respiratory tract, especially bronchitis and pneumonia. According to these observations it apparently plays at certain seasons a more important part than the pneumococcus. The cultures indicate that the *B. influenzae* and the pneumococcus are associated in a very large number of patients. I believe that this mixed infection of influenza with the pneumococcus has greatly modified the clinical course of our acute pneumonias as we see them to-day. The clinical picture may be determined in one case by a predominance of influenza, in another by a predominance of pneumococcus infection. It may be difficult, and perhaps, in most cases, impossible to separate the two factors. But that there is such a pathogenic and clinical entity as influenza from our experience seems certain.

With respect to apparently healthy persons whose bronchial or pharyngeal secretions contain the *B. influenzae*, we are in exactly the same position as with persons who in a similar way harbor the pneumococcus. Who shall say that either is not a menace to those with whom such a person is thrown in close contact? Among persons examined in the course of these observations, there were found sixteen healthy persons whose secretions showed the *B. influenzae*, often in pure culture and repeatedly, fifteen of these were nurses. Of these sixteen persons, eight showed also the pneumococcus and four had diphtheria bacilli. One nurse gave positive influenza cultures on April 30, May 5, 10, 12, 18 and 28, but later this organism was not found. In several of these examinations there was a pure growth.

I confess I am strongly inclined to regard such persons as probable carriers of infection, to be treated accordingly. It is only by the recognition and removal of such obscure etiological factors that we shall succeed in limiting house infections. This raises many practical questions regarding quarantine and isolation which with our present knowledge are difficult to answer. But our eyes should certainly be open to cases of this kind, which I believe to be a very real source of danger.

Positive pneumococcus cultures without influenza were obtained in twenty apparently healthy persons eleven being nurses, in many of

<sup>1</sup> This has however been found by us in one case since that time.

them, repeatedly. In about half of the healthy inmates of the hospital examined in the winter months either the pneumococcus or the *B. influenzae* was found, and in one-half neither was present.

#### THE CLINICAL FEATURES OF INFLUENZA INFECTIONS

These observations indicate that there is no single clinical type which we may always diagnosticate influenza, that it is not often the acute catarrhal symptoms of the upper respiratory tract, but certain constitutional and certain bronchopneumonic symptoms. The constitutional symptoms are often characterized by rather high and widely fluctuating temperature of a remittent or intermittent type, but without a corresponding amount of general prostration. The temperature seems to have no regular course, it may last only two or three days or may run as many weeks even without the development of inflammatory complications, which, however, are very prone to occur.

The bronchopneumonic symptoms are sometimes early and apparently primary, but more often secondary and late. They are frequently severe and threatening, but of a very evanescent character. At other times they are protracted and tend to chronicity with frequent exacerbation of acute symptoms, indicating a persistence of the infection. This latter form is frequently seen in children of feeble resistance.

There are other inflammations accompanying influenza which are to be regarded in the light of complications. A frequent one is otitis. In eighty-five persons giving positive influenza cultures there were seventeen of acute otitis. It will be recalled that in no one of the twenty-nine cultures made after fresh paracentesis was the *B. influenzae* found. It is easy to see, then, why this operation, while relieving the local inflammation, not only does not cause the temperature to fall to normal, but may not affect the temperature at all. The operation has no effect on the general influenza infection. This is a point which those who regard a persistent elevated temperature after paracentesis has been done as a sign of mastoid disease, will do well to consider. I have with difficulty on several occasions restrained the aural surgeon from opening the mastoid or excising the sinus or jugular vein—in no instance, I am happy to say, to the detriment of the patient.

I have recently seen five cases of acute nephritis and rarely acute pyelitis as a complication of influenza, especially when persistent, occurring just as they might occur after scarlet fever or measles.

The *B. influenzae* being chiefly found in the lower respiratory tract, it is easy to see why gargles and mouth-washes proved so unsatisfactory.

as a means of getting rid of the organism from the secretions. When once firmly established in the bronchial mucous membrane it seems most difficult to get rid of it, especially in persons whose general condition is below par. This explains the resistant character of influenza attacks in such patients, also the recurrences when the disease is apparently at an end, and the marked influence of change of climate in curing these patients. In cases seen in the winter or spring in New York sometimes nothing but removal to a warm climate will break up these attacks, but it is surprising how quickly persons often recover when such a change is made. I once regarded these recurrences as reinfections from without, sometimes from the apartments or from other persons, but in the light of the culture findings my present belief is that such patients have never become free of the organism from the bronchi and that these under favorable conditions continue to excite relapses.

These observations shed light on certain irregular features of acute bronchopneumonia, especially cases in which a high and widely fluctuating temperature occurs. Persistent temperature may occur from influenza infection without important signs in the chest or other evidences of local inflammation. A knowledge of these peculiarities of the temperature curve in influenza should make one very cautious in inferring that because a child with acute otitis, for instance, has a persistent and widely fluctuating temperature, such temperature, provided pneumonia can be excluded, depends on the ear condition or its complications, mastoiditis or sinus thrombosis.

In the management of the protracted cases nothing can be worse than crowding and the confinement in close rooms or wards. Fresh air in abundance is indispensable. Regarding the effect of the very cold air in hospital wards for such patients, I am not quite so sure. If it can be secured without exciting fresh catarrhal attacks it may be desirable, but this risk is considerable. The extreme susceptibility of these patients should be remembered, and I have in several instances seen an attack of pneumonia which seemed to be traceable to such an exposure in cold-air treatment. Cold wards are, I believe, of much greater value in preventing these respiratory infections from gaining a foothold than in curing them when once established.

#### CONCLUSIONS

- 1 The use of the term influenza should be limited to an inflammation or infection excited by Pfeiffer's bacillus
- 2 It is of great importance in all infections of the lower respiratory tract, especially during the cold weather

3 It has very much less to do with acute nasopharyngeal cataracts and their complications, otitis, adenitis, etc

4 It may cause severe general symptoms with few or no local symptoms, even of the respiratory tract, but general blood infection with this organism is very rare<sup>5</sup>

5 While in most patients the influenza infection causes acute symptoms only, recurrences are exceedingly common, and in some patients the attacks are prolonged, persisting for months

6 The *B. influenzae* may be harbored in the secretions of apparently healthy persons for a considerable period, certainly for several weeks, whether such persons may spread the disease is not yet determined

7 If properly made, cultures are of great value for diagnosis, but the bronchial secretion should be secured

The foregoing is to be regarded as a preliminary report, as the study is still going on, and many more observations will be necessary before definite conclusions can be reached

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## A MODIFIED METHOD FOR THE CLINICAL ESTIMATION OF PEPSIN

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In the chemical examination of stomach contents attention has lately been directed anew to the estimation of the enzyme content of the gastric secretion, and a number of relatively simple methods of analysis have been proposed. Among these are the methods of Volhard,<sup>1</sup> Fuld and Levison,<sup>2</sup> Gross,<sup>3</sup> and Jacoby and Solms.<sup>4</sup> The Jacoby-Solms procedure appears to offer the greatest advantages, and has received favorable consideration for clinical purposes in this country from Goodman<sup>5</sup> and Einhorn,<sup>6</sup> and abroad from Witte<sup>7</sup> and others. The method involves the preparation of an imperfect solution of commercial "ricin" (prepared from the castor bean). This fluid is rendered more turbid by addition of a small amount of acid. Diluted gastric contents are added in varying quantity to a series of test-tubes containing the same volume of the turbid ricin solution, and after the total volumes of fluid are made alike in all the tubes they are allowed to stand in an incubator for three hours.<sup>8</sup> At the end of this time one examines the tubes to ascertain with what dilution the cloudy solution has cleared up, i.e., in which tube the suspended protein has just been completely dissolved by the enzyme present. The pepsin content of 1 cc. of gastric juice which, in a dilution of 1 to 100, is just capable of carrying out the reaction as outlined, is expressed as 100 pepsin units. On this basis the enzyme content of variously diluted gastric contents can be calculated.

\* From the Sheffield Laboratory of Physiological Chemistry, Yale University.

1 Volhard Munchen, med Wehnschr., 1903, L, 2129

2 Fuld and Levison Biochem Ztschr., 1907, vi, 473

3 Gross Berl klin Wehnschr., 1908, xlvi, 643

4 Solms Ztschr f klin Med., 1907, lxxiv, 159

5 Goodman Am Jour Med Sc., 1908, cxxxvi, 734

6 Einhorn Berl klin Wehnschr., 1908, xlvi, 1567, New York Med Rec., 1908, lxxiv, 351

7 Witte Berl klin Wehnschr., 1907, xlvi, 1338

8 Einhorn (Berl klin Wehnschr., 1908, xlvi, 1567, New York Med Rec., 1908, lxxiv, 1338) uses a glass vacuum bottle instead of a thermostat for heating the tests. The vacuum bottle contains twelve graduated pepsin tubes showing marks at 2 cc., 3 cc., and 3.5 cc. By this means he dispenses with pipettes. The whole apparatus is filled with water having a temperature of 50 or 60 C., well corked, and digestion allowed to continue for thirty minutes.

In principle the process really consists in obtaining a saline extract of the crude "ricin," containing sufficient globulin to yield an incipient protein precipitation on addition of very small quantities of acid. This behavior is in no way specifically characteristic of the proteins of the castor bean (*Ricinus*). The precipitation of most seed proteins by acid depends largely on the presence of inorganic salts in their solutions.<sup>9</sup> The selection of the so-called ricin for the pepsin test is an unfortunate one. The commercial product is not always readily available, although Jacoby has suggested a source of supply in Berlin. The purchasable preparations are crude mixtures of varying and inconstant make-up, containing considerable insoluble denatured protein (probably proteans). But the most serious objection lies in the extreme toxicity of castor bean products. This is shown in the studies of Osborne, Mendel, and Harris<sup>10</sup> with the purified protein ricin isolated by them from *Ricinus* seeds. Fractions of a milligram of pure ricin will kill a rabbit, and the necessity for care in handling such a product has not been properly emphasized.

Furthermore, true ricin is an albumin, as the researches mentioned have shown, and proteins of the globulin type are better adapted for the preparation of cloudy solutions. Indeed, the Jacoby-Solms reaction with castor bean proteins should properly receive some designation other than the "ricin test."

A globulin preparation well adapted for the purpose of the Jacoby test can be made cheaply from the ordinary garden pea, *Pisum sativum*, as follows. The finely ground peas, freed as much as possible from the outer coating, are repeatedly extracted with large quantities of 10 per cent sodium chloride solution, the extracts combined, strained through fine bolting-cloth, and allowed to stand over night in large cylinders to deposit insoluble matter. The supernatant fluid is siphoned off and saturated with ammonium sulphate. The precipitate of albumins and globulins is filtered off, suspended in a little water, and dialyzed in running water for three days, until the salt has been removed, and the albumins have been dissolved. The globulins are filtered off and washed two or three times with water to remove the last trace of albumins. To purify further, the precipitate is extracted with 10 per cent sodium chloride solution, and filtered until perfectly clear. The resulting solution is exactly neutralized to litmus paper by the cautious addition of dilute sodium hydroxide, and again dialyzed in running water for three

<sup>9</sup> Cf. Osborne, The Vegetable Proteins, 1909.

<sup>10</sup> Osborne, Mendel, and Harris, Am. Jour. Physiol., 1905, xiv, 259. Cf. also B. W. McFarland, Yale Med. Jour., 1910, vii, 379.

days to remove the salts completely. The precipitated globulins are then filtered off, and dried on a water-bath at 40° C. During the complete process of separation the proteins should be preserved with a mixture of alcoholic thymol and toluene. The globulins so prepared dissolve practically completely in 10 per cent sodium chloride solution, and after slight acidification with hydrochloric acid yield a turbid solution, which does not settle out on standing.

Since in the Jacoby-Solms method the stomach contents are not neutralized, the estimations are not made under like conditions of acidity. It was thought advisable, therefore, to modify the method in this respect also, and to make all digestions in a solution whose total acidity is 0.2 per cent of hydrochloric acid. By this means one determines not the digestive power of the gastric fluid, but the relative amount of pepsin present. The necessity of knowing whether or not the gastric juice in question is normal in respect to acid before diluting is also avoided.

#### METHOD

The complete method as modified follows. 0.25 gm. globulin of the pea, prepared as described above, is dissolved in 100 cc of 10 per cent sodium chloride solution (by warming slightly if necessary) and filtered.<sup>11</sup> Portions of the clear filtrate of 1 cc each are introduced into a series of eleven small test-tubes about 1 cm in diameter. To each tube is added 1 cc of 0.6 per cent hydrochloric acid, and about five minutes are allowed for the development of the turbidity. A measured volume of the stomach contents is then exactly neutralized to litmus paper with dilute alkali. If a precipitate of acid protein forms, this is filtered off, and the clear neutral solution is diluted a known number of times (usually five) with distilled water, allowance being made for the dilution of neutralization. A portion of the diluted juice is boiled and filtered, and amounts decreasing by 0.1 cc added to the tubes of turbid protein to the first, 1.0 cc to the second, 0.9 cc, to the third, 0.8 cc, and so on to the eleventh, to which none is added. The unboiled juice is then rapidly added in increasing amounts as follows to the first, none, to the second, 0.1 cc, to the third, 0.2 cc, to the fourth, 0.3 cc, to the fifth, 0.4 cc, to the

<sup>11</sup> Such a solution will keep perfectly well for two months if covered with a thin layer of toluene. At the end of that time, acidification produces no more turbidity than when freshly prepared solutions are used. This avoids the objection raised against the Jacoby-Solms method by Farr and Goodman (*THE ARCHIVES INT MED*, 1908, 1, 648). These authors, while in general considering the method favorably, point out that solutions of commercial ricin which have been prepared for some time are rendered so much more turbid by the addition of acid that fresh solutions must always be employed.

sixth, 0.5 cc., to the seventh, 0.6 cc., to the eighth, 0.7 cc., to the ninth, 0.8 cc., to the tenth, 0.9 cc., and to the eleventh, 1.0 cc. Each of the tubes thus has a total volume of 3.0 cc., and a total acidity of 0.2 per cent of hydrochloric acid, as shown in the following scheme

Tubes	1	2	3	4	5	6	7	8	9	10	11
0.25 % globulin solution, cc	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
0.6 % HCl, cc	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Boiled gastric juice, cc	1.0	0.9	0.8	0.7	0.6	0.5	0.4	0.3	0.2	0.1	0
Unboiled gastric juice, cc	0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
Total volume, cc	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
Total acidity, % HCl	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2

The measurements of the solutions may be easily and accurately made with a pipette of 1 cc. capacity, graduated to 0.01 cc. The tubes are well shaken and allowed to stand in a thermostat or water-bath for fifteen minutes at a temperature of 50 to 52 C. Exactly the same endpoint is obtained by keeping the tubes at a temperature of 35 or 36 C for one hour. At the end of the digestion time that tube in the series is selected which contains the least amount of gastric juice and which exhibits no turbidity. The peptic activity is calculated on the basis of the amount of gastric juice used in this tube. The enzyme content is expressed by the number of cubic centimeters of the 0.25 per cent globulin solution that would be digested by 1 cubic centimeter of the undiluted gastric juice under examination, if the activity were exerted for a period of one hour at 35 or 36 C, or for fifteen minutes at 50 or 52 C. For example, if 0.5 cc. of a gastric juice diluted five times clears up one cubic centimeter of the 0.25 per cent globulin solution in fifteen minutes at the given temperature, the activity of the solution would be expressed

$$\text{Peptic activity} = (1 - 0.5) \times 5 = 10$$

For clinical purposes it suffices to use the scale of pepsin units here proposed, which gives figures about one-tenth of those expressed on the Jacoby-Solms scale. Lately it has been found that six tubes ordinarily afford a range of trial which suffices for all diagnostic purposes.

#### SCHEME OF SIX TUBES

Tubes	1	2	3	4	5	6
0.25 % globulin solution, cc	1.0	1.0	1.0	1.0	1.0	1.0
0.6 % HCl cc	1.0	1.0	1.0	1.0	1.0	1.0
Boiled gastric juice, cc	1.0	0.9	0.7	0.5	0.2	0
Unboiled gastric juice, cc	0	0.1	0.3	0.5	0.8	1.0
Total volume, cc	3.0	3.0	3.0	3.0	3.0	3.0
Total acidity, % HCl	0.2	0.2	0.2	0.2	0.2	0.2

In the above method the conditions are constant in every trial, in respect to acidity, volume, protein content, and temperature. One determines the proteolytic activity of the gastric filtrate independently of the variations in acidity. Thus an additional variable of the original Jacoby-Solms procedure is eliminated. Goodman<sup>5</sup> concludes from a limited number of observations that uniform acidity makes no difference in the final result. Using the method here proposed, I am unable to accept these conclusions. Several series of tests showed that, while variations within the normal range of acidity produced no difference in the final results, large decreases, such as occur pathologically, have a marked influence on the rapidity with which the turbid solutions are cleared. The results of two typical series of tests, one made with artificially prepared gastric juice, and the other with normal human gastric juice, are shown in Table 1.

TABLE 1.—TESTS WITH HUMAN AND ARTIFICIAL GASTRIC JUICE

Artificial Gastric Juice		Human Gastric Juice	
Acidity	Pepsin Content	Acidity	Pepsin Content
0.4 % HCl		0.4 % HCl	10
0.2 % HCl	14	0.2 % HCl	10
0.1 % HCl	14	0.1 % HCl	10
0.05 % HCl	18	0.05 % HCl	15

It will be seen that the enzyme content is expressed by much larger numbers when the total acidity is 0.05 per cent of hydrochloric acid than when it is 0.2 per cent. This is not due to greater activity of the pepsin under such conditions, but to the decreased turbidity of the globulin solution, resulting from the decreased acidity. Less enzymolysis is necessary for the clearing of the solution, since the cloudiness is so much less intense. When the acidity is further decreased, the loss in peptic activity far overbalances the loss in turbidity, with the result that much smaller figures are obtained.

In the Jacoby-Solms method the total acidity in the tubes is frequently as low as 0.05 per cent of hydrochloric acid. In many pathological conditions, such as pernicious anemia, gastric carcinoma, gastric diseases of children, etc., the acidity is practically or absolutely nil.<sup>12</sup> If the unmodified test method is employed in such cases, the acidity in the tests will be only that resulting from the addition of the 0.5 c.c. of tenth-normal hydrochloric acid, used to render the protein solutions turbid. Errors in analysis will then probably occur. Indeed, Witte<sup>7</sup> found, using

12 See Willecox (*Quart Jour Med.*, 1909, III, 93-106), for a review of the literature on acidity of the gastric juice in various diseases.

the Jacoby procedure, that the enzyme activity was much reduced by neutralizing the samples of stomach contents before making the determinations Nirenstein and Schiff<sup>13</sup> and Roth,<sup>14</sup> in studying the composition of the gastric secretion under various conditions with the Mett method, also recognized the importance of the hydrochloric acid content on the enzymatic activity. They state that for comparable results all estimations must be made under like conditions of acidity.

TABLE 2—RESULTS OF ANALYSIS MADE BY PROPOSED MODIFICATION

Sample	Diagnosis	Peptic Activity	Remarks
1	Normal	10	
2	Normal	10	
3	Normal	10	
4	Normal	9	
5	Normal	11	
6	Practically normal	10	
7	Practically normal	10	
8	Practically normal	10	
9	Practically normal	10	
10	Constipation	9	Acidity very low
11	Hypoacidity	10	
12	Nervous hypoacidity	10	
13	Nervous hypoacidity	10	
14	Hyperacidity	12	
15	Gastritis	10	No free hydrochloric acid
16	Neurasthenia	10	Very low acidity
17	Neurasthenia	10	No free hydrochloric acid
18	Gastric ulcer	12	Very high acidity
19	Ulcer of duodenum	10	High acidity
20	Gall stones	3	
21	*Gastric carcinoma	2	
22	Gastric carcinoma	1	Young man, 26 years old
23	*Gastric carcinoma	Trace	No free HCl Rennin negative
24	Gastric carcinoma	Trace	
25	*Carcinoma of intestine	3	Young woman, 24 years old No free HCl
26	Carcinoma of esophagus	2	
27	*Cancer of the rectum	10	
28	*Cancer of the breast	2	Total acidity, 42 No free HCl

\* Diagnosis verified by operation

13 Nirenstein und Schiff Arch f Verdauungskl., 1902, VIII, 559

14 Roth Ztschr f klin Med., 1900, XXXIV, 1

In the tabular scheme (Table 2) the results of analysis made by the proposed modification are summarized. The gastric contents were withdrawn after an ordinary Ewald test meal<sup>15</sup>.

It will be noted that the "normal" peptic activity on the scale here proposed is about 10, corresponding with the figure 100 on the scale of Jacoby and Solms. No attempt has been made to select cases illustrative of the incidence of peptic activity in various diseased states. The characteristic low figures in carcinoma are typically shown.

The possible presence of an antienzyme should be taken into consideration in making an examination of the gastric secretion. Oguro<sup>16</sup> has shown that blood-serum contains an antipepsin, which may be demonstrated by heating the neutralized gastric juice with the serum at body temperature. It is advisable, therefore, before estimating the proteolytic activity, to make a test for blood in stomach contents containing little or no free hydrochloric acid.

I wish to express my gratitude to Prof. Lafayette B. Mendel, at whose suggestion and under whose guidance the study was made, for much helpful advice.

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15 Most of the specimens were furnished by Dr. L. M. Gomperz, instructor in gastroenteric diseases, who made the clinical diagnosis in each case.

16 Oguro Biochem Ztschr., 1909, xxii, 266-277

## FURTHER STUDIES ON THE INFLUENCE OF THE DUCTLESS GLANDS ON THE PANCREAS

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In some recent contributions<sup>1</sup> we published the results of investigation, extending over about two years, on pancreatic activity, which led to the following, among other, conclusions

The suprarenal and pituitary bodies of dogs contain something which, on injection into other dogs, inhibits the flow from the pancreas when excited by secretin. This inhibitory substance can be extracted by salt solution and has been found as yet in no other tissue of the body.

Inhibition occurs whether the extracts be injected before, coincidently with, or after the injection of secretin, and we ventured the tentative view that it was independent of the general blood-pressure.

Our method of recording the flow from the pancreas is by means of a graduated cannula in the duct of Wirsung. As the juice flows past the divisions on the cannula its motion is recorded on the base line of a revolving drum supplied with a so-called endless roll of paper. Coincident tracings are taken of blood-pressure, respiration, and time in seconds. (Details of technic are given in the papers cited in Note 1.)

We have this year extended our observations and have found beyond question that the inhibition of the pancreatic flow seen after adrenalin, at least, is independent of the systemic rise in blood-pressure. Edmunds<sup>2</sup> has recently repeated some of our work, has obtained the same general results, and ascribes the inhibition solely to the rise of pressure. We have many records in which, after an inhibition injection of adrenalin, the blood-pressure has been made to fall by an exciting dose of secretin to below its normal level, and yet no adequate response has been

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1 Pemberton, Ralph, and Sweet, J. E. The Inhibition of Pancreatic Activity by Extracts of Suprarenal and Pituitary Bodies, THE ARCHIVES INT. MED., 1908, I, 628, and II, 295.

2 Edmunds. The Antagonism of the Adrenal Gland Against the Pancreas, Jou. Pharmacol. Exper. Therap., 1909 I, 135.

obtained, even following a second or third injection. In other words, the inhibition may persist a variable time, though the systemic blood-pressure has fallen to normal or considerably below. In all such experimentation it is evident that a certain balance between the amounts of the two factors must be found and maintained. A very large amount of secretin, relative to the amount of adrenalin, may completely mask the inhibition exhibited by the latter under the conditions of a balanced experiment.

Making use of disproportionate quantities, it is frequently possible to obtain, even with a moderate amount of secretin, an active pancreatic flow when the blood-pressure is raised to its maximum by adrenalin (Fig. 1). Also transfusion of the blood of a healthy dog modifies not at all the flow from the pancreas, even though the vascular system be engorged and the pressure made to rise by that means, as will be noted again later.

Furthermore, in using preparations of our own manufacture and comparing them with a commercial standard, we have noticed that solutions of suprarenal extract which raise the general blood-pressure to identical heights may exercise differing effects on the pancreas, suggesting that there is some factor at stake other than the rise of blood-pressure. Certain extraneous substances, as nicotin, may produce somewhat similar results, but the point of importance in this connection is that the body itself should contain agents of this nature. The exact *modus operandi* and the variety of extraneous factors which can so operate are manifestly of importance secondary to establishing the fact that such an interglandular correlation of action exists. We shall refer to this later.

As a further extension of our studies we investigated the question of whether the inhibition from adrenalin and the pituitary extracts also occurs when the pancreas is excited by means other than secretin. We have yet to try in this connection the effects of the suprarenal and the pituitary extract after stimulation of the pancreas by gastric chyme obtained from a fistula in an otherwise sound dog, but, whatever the result of this may be, it is clear that these inhibitory agents exercise the same influence on the flow which follows the introduction into the duodenum of hydrochloric acid as on that following secretin. (It is unnecessary to repeat here the details of our technic in establishing and measuring the flow of pancreatic juice and its inhibition. They are essentially as given in our past contributions on this topic<sup>1, 3</sup>) Under the conditions of stimulation by hydrochloric acid, the glandular activity is longer con-

<sup>3</sup> Sweet, J. Edwin, and Pemberton, Ralph. Experimental Observations on Secretion with Special Reference to Diabetes and Malnutrition, THE ARCHIVES INT MED., 1908, 1, 231.

tinued, slower to occur and less violent, but inhibition is apparently as marked as at other times Secretion from this stimulus is, of course, not accompanied by a fall of blood-pressure

It is also plain that the properties of adrenalin under discussion are probably features of the large molecule to which the blood-pressure-raising principle is ascribed This seems evident as the result of some work with a synthetic suprarenal extract, which is stated to be a chemical compound corresponding identically with the active features of adrenalin and having the same generally recognized properties From it we obtained the same results as those which followed the use of the ordinary gland extract slowing of the pancreatic flow after excitation, together with inhibition when given before stimulation

In the course of some experiments, as yet incomplete, connected with the transfusion of diabetic blood, we have transfused a pancreas which was removed, together with the intestines and portal vein, from a previously sound dog A cannula was placed as usual in the common duct, the eviscerated organs were placed in warm salt solution and anastomosis was established between the aorta and the portal vein just mentioned, on the one hand, and the carotid and jugular, respectively, of another sound dog, on the other A cannula was also placed in the pancreatic duct of the sound dog An injection of secretin into the donor caused the pancreas of each dog to respond distinctly

Again, as referred to earlier, the carotid of one healthy dog was united with the femoral of another dog whose pancreas was under observation and, while the gland was responding actively, though not violently, blood was allowed to flow from the donor The manometer in the femoral artery of the recipient showed a rise in blood-pressure and, after subsidence of the pancreatic activity, while blood was still flowing in, other injections of secretin were given and always with the same results The response seemed to bear no relation to the rise of blood-pressure thus obtained On exsanguination of the donor the recipient was killed and its tissues found to be in the highest degree hemorrhagic and everywhere greatly congested Notwithstanding this, the pancreatic juice had flowed freely until almost the end The actual rise in blood-pressure was not so great as is generally seen after adrenalin, but was comparable to some instances in which we have had inhibition It therefore becomes plain that, if inhibition be accredited to a rise in blood-pressure, the rise must be local at the pancreas, producing some manner of injury to the secreting structures, and must be quite independent of the general pressure Some evidence opposes this hypothesis, namely, that a rise in blood-pressure is the sole agent, and only recently it has been shown, for

example, that adrenalin actually antagonizes the inhibitory action of atropin on the secretory glands of the skin and so far fails to inhibit activity that the atropin administered can be detected in an increased secretion.

After investigating some of the factors which may produce inhibition of pancreatic secretion, Edmunds considers stimulation of the splanchnics and says:

The result produced (by stimulation of the splanchnics) was a great increase in the blood-pressure and inhibition of the secretion. The changes were almost the same as those brought about by asphyxia in that the effect comes on more slowly than with the drugs, and is not nearly as complete, even when the blood-pressure may be raised to an equal extent. In one instance there was very little retardation, but in every other trial, if the period of stimulation was continued more than a minute, the rate of secretion was reduced from 25 to 50 per cent.

If the inhibition is due merely to change in the circulation, one point which is not quite clear is that, although the blood-pressure may be raised to the same height by chemical action or by nerve stimulation, yet the inhibition which is produced by adrenalin or by nicotin is very much more complete than that produced through asphyxia or electrical stimulation. The most reasonable explanation which suggests itself is that the two drugs may cause more constriction of the vessels of the pancreas than does splanchnic stimulation and thus greater anemia results from their use.

Several points here require consideration. In the first place Edmunds records with a tracing an instance of a great increase in blood-pressure with inhibition and says that the effect (inhibition) comes on more slowly than with drugs and is not nearly so complete, even when the blood-pressure is raised to an equal extent. This has been exactly our experience, that agents with similar power of raising blood-pressure do not necessarily exercise the same amount of inhibition, and such an observation strongly indicates that some other factors may be operating.

Indeed, Edmunds' experiments have adduced by other means some of the very facts which we have advanced as evidence in some of our papers.

Furthermore, he records instances of inhibition which we have not felt were quite worthy of consideration as such. When we have spoken of inhibition, we have meant a definite and unmistakable decrease, amounting almost or quite to cessation, about which there could not be the slightest doubt whatever. Such cannot be said of instances in which "the rate of secretion was reduced from 25 to 50 per cent," and his tracing<sup>4</sup> advanced in support of this as an example of inhibition shows such a trifling decrease that there seems to be ground for question as to whether it exists at all. Such a record is hardly comparable to the prompt, marked and vigorous inhibition caused by adrenalin or pituitary.

4 Tracing 4, on page 146

extract, not to mention the almost total lack of flow which occasionally succeeds this even after repeated injection of secretin, furthermore, the recorded inhibition was of a leisurely secretion compared with the active responses which we have discussed. And then, again, to assume, as in the last paragraph, that "the two drugs, adrenalin and nicotin, may cause more constriction of the vessels of the pancreas than does splanchnic stimulation and thus greater anemia results from their use," merely advances another hypothesis and directs attention to the very phenomenon which we have elsewhere previously noted.

It is desirable to emphasize, since the opposite contention has been imputed to us, that nowhere have we denied that inhibition of the pancreas by adrenalin may be caused by a local change in blood-pressure at that organ. Our conclusions were that such inhibition was independent of the general blood-pressure, which we still maintain. We are personally prepared to believe that the former may conceivably be the case, though this has not yet been shown. Incidentally the action of adrenalin so varies on different structures, increasing skin secretion while it inhibits salivary, for example, that no dependable analogy can be drawn from its action on any particular part. It is manifestly unreasonable, as we elsewhere pointed out,<sup>5</sup> to compare the effect of a systemic injection of a small dose of adrenalin into the jugular, with the direct application of it to the surface of the gland, a comparison that has been made in considering the pros and cons of the question.

In defense of the hypothesis of inhibition by blood-pressure alone it seems that we have but two alternatives, viz.

1 The theory that the injection of adrenalin so injures the tissue of the pancreas by the vasoconstriction that no glandular activity is possible (though it returns later), even when the system as a whole has plainly recovered.

2 The hypothesis that, although the general systemic blood-pressure has been made to fall to its minimum by exciting doses of secretin, nevertheless the blood-vessels of the pancreas are constricted to their utmost, and the local blood-pressure at the same time maintained at practically its maximum. Either of these hypotheses alone fails to bring conviction from the data now at hand, and the latter is tantamount to assuming a specificity. The nervous control of the blood-vessels which supply the pancreas is probably definite and delicate and susceptible to influence by a variety of factors. The atmosphere is not well cleared however, by throwing on this mechanism the discriminating burden of affecting differently the external secretion of the gland, according as one

<sup>5</sup> THE ARCHIVES INT MED., 1908, 1, 628

or another agent is used to raise the blood-pressure, especially when each agent has apparently identical vasomotor effects, and is followed by the same apparent rise of blood-pressure.

Again, in his conclusions, Edmunds says "The action of adrenalin in inhibiting the pancreatic secretion cannot be considered in any sense as specific." We have never asserted that it is absolutely specific, but there has been no evidence adduced, nevertheless, that it is not specific. That nicotin should produce inhibition no more concerns the question of specificity than does trauma by violence from without. The healthy body does not contain nicotin and it does contain adrenals. If it can be shown that extracts of tissues other than the adrenals or the pituitary gland can produce such inhibitory results, then just doubt of specificity can arise, but not until then.

Even though inhibition be caused, for argument's sake, by vasoconstriction alone, the "specificity" of this action is at present in no way less evident.

Edmunds himself finds that "the efficiency of the pancreas is probably very closely connected with the blood-supply." It is, therefore, hard to see how he can reject the possibility of some control over its activity by the adrenals, in view of the evident and conspicuous effect which they exercise experimentally and the important circulatory rôle which they are known to fill in the economy. Furthermore, constantly accumulating evidence, much too voluminous to quote here, indicates almost without question a very intimate association of the two organs, and to view as accidental the phenomena under discussion is to turn away from the trend of evidence.<sup>6</sup>

As indicated earlier in this paper, we have had under consideration for some time experiments bearing on certain possible relations of the pancreas to diabetes and, for the purpose to be mentioned presently, have produced experimental diabetes in a number of dogs by extirpation of the pancreas. All of the dogs so treated were kept under observation in a metabolism cage, pending the development of those symptoms of glycosuria, acidosis, emaciation, and so on, which usually follow. When the artificial diabetes was well pronounced the animals were killed and preparations of secretin made from the upper four feet of the small intestine according to our usual technic. A weighed amount of intestinal scrapings was treated with a definite amount of 0.4 per cent hydrochloric

<sup>6</sup> Since this article was written, a brief note, without details, has appeared (*Science*, 1909, **xxi**, 237), stating that the inhibition of pancreatic activity is due to a vasoconstriction which may persist in the pancreas longer than does the general vasoconstriction elsewhere. If this be true, it would seem to substantiate the idea of the specificity of action of the adrenals and the pituitary gland.

acid and, at the same time, a control preparation made from a normal animal just killed. The scrapings made from the normal animal were also weighed and treated with a proportionate amount of hydrochloric acid, so that the resulting solutions were of the same strength, weight for weight. Now a dog which has been rendered diabetic by extirpation of its pancreas bears no comparison physically, a week after the operation, to a sound dog of the same relative size. The former becomes greatly emaciated as a result of its diabetic processes, whether or not its appetite be good, the organs are the seat of secondary disease, as, for example, fatty degeneration of the liver, and all the fat disappears in those cases in which the typical picture supervenes. The mesentery especially is lacking in its usual fat content, so that on stripping the entire bowel of its mesentery preparatory to scraping the mucosa it comes away cleanly and easily in contrast to that of a normal animal. On opening the intestine the mucosa is found surprisingly abundant and seems at times to be greater in amount, not only relatively but also actually, than that seen in the normal intestine. In such an animal we had in mind a lowered content or efficiency of prosecretin in the intestine, because of the conceivable preponderance of some suprarenal factor in the absence of the pancreas. Contrary, however, to what might be expected, the mucosa is abundant and it is easy to prepare secretin from it. The interesting feature in connection with such a preparation is that a solution so made up has stimulating power fully equal to those from the intestine of a healthy dog, and, indeed, there is sometimes reason to believe that the latter are exceeded. Our responses from the pancreas after injection of 5 or 10 c.c. of these solutions always showed an output of pancreatic juice as the result of the "diabetic" secretin, quite as prompt to begin, quite as violent in action, and quite as long continued as those following the normal solutions. Indeed, as mentioned above, they sometimes considerably surpassed the controls.

From this we must conclude that, whereas, with the dog rendered diabetic by extirpation of its pancreas, the organism as a whole wastes visibly and there occur great loss of nitrogen, profound weakness and marked degenerative changes in the organs, nevertheless the intestinal mucosa remains apparently unaffected, "prosecretin" is as abundant as in health, and it would seem as though in the absence of the pancreas to utilize and destroy the secretin formed for its stimulation, a residue of the latter remained unused, perhaps in quantities greater than normal. We have made as yet no studies in this connection, on dogs the subject of other disease, although in a previous paper<sup>3</sup> we pointed out that simple fasting for five days produced no diminution in the prosecretin of dogs.

It might be pertinent to mention, however, that we have found a difficulty in obtaining secretin from the intestines of human beings the seat of various conditions and, if we can reason by analogy, we have in this abundance of mucosa found in dogs profoundly and fatally ill as are those the subject of our remarks, a departure from the customary state of affairs in at least some wasting diseases.

One of the most interesting topics with which we have been concerned this year, however, is the relation of the thyroid and the parathyroids to the pancreas and to some of the influences to which the latter is subject. A number of relations have been reported in this connection. Marinesco and Parhan have found a diminution of the lipochrome in the zona fasciculata of the suprarenals in dogs dead from tetany, the result of thyroidectomy. Pick and Pineles assert that extirpation of the thyroid hinders the appearance in young goats of adrenalin glycosuria, which can be easily caused in animals not operated on, though the diuresis and blood-pressure rise from adrenalin are not influenced in such goats or hares. R. Hirsch has shown that after complete thyroidectomy the assimilation limit for dextrose given by mouth is significantly decreased, and he has also pointed out, with others, that the thyroids and parathyroids differ in their influence on carbohydrate metabolism. Eppinger, Falta, and Rudinger assert that in thyroidectomized dogs adrenalin causes less glycosuria than it does under ordinary conditions, but after removal of both the thyroid and parathyroids adrenalin causes glycosuria as usual. Recently, however, Underhill and Hilditch<sup>6</sup> have gone over the work of Eppinger, Falta and Rudinger and reach opposite conclusions. They advance evidence to show that, with at least two parathyroids intact, the removal of the thyroids and remaining parathyroids does not alter the susceptibility of the animal to adrenalin glycosuria. It has also been indicated by their work and that of others that removal of both thyroids and parathyroids does lower the body capacity for assimilating sugar. The statement of Eppinger, Falta and Rudinger, that adrenalin behaves as usual toward dogs the subject of thyroparathyroidectomy carries less weight in view of the opposite findings of Underhill and Hilditch in regard to the behavior of adrenalin toward thyroidectomized dogs. A not insignificant part of these conflicting data on this subject has appeared since we began the investigation presently to be described. If, therefore, there be some relation between the thyroids, parathyroids and pancreas, whereby the removal of the influence of the two former prevents or decreases the usual assimilation of sugar, and if, as we have elsewhere shown, there is a marked inhibition of the external pancreatic

<sup>6</sup> Underhill and Hilditch Am Jour Physiol, xxx, 66

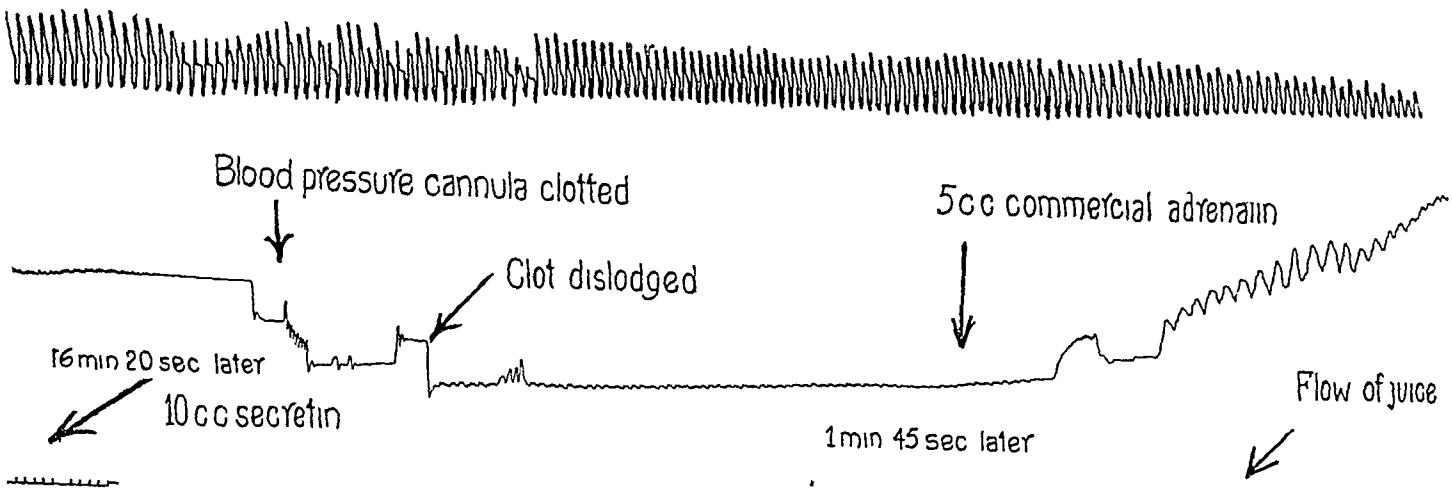


Fig 1.—Tracing, made April 27, 1909, showing relatively slow

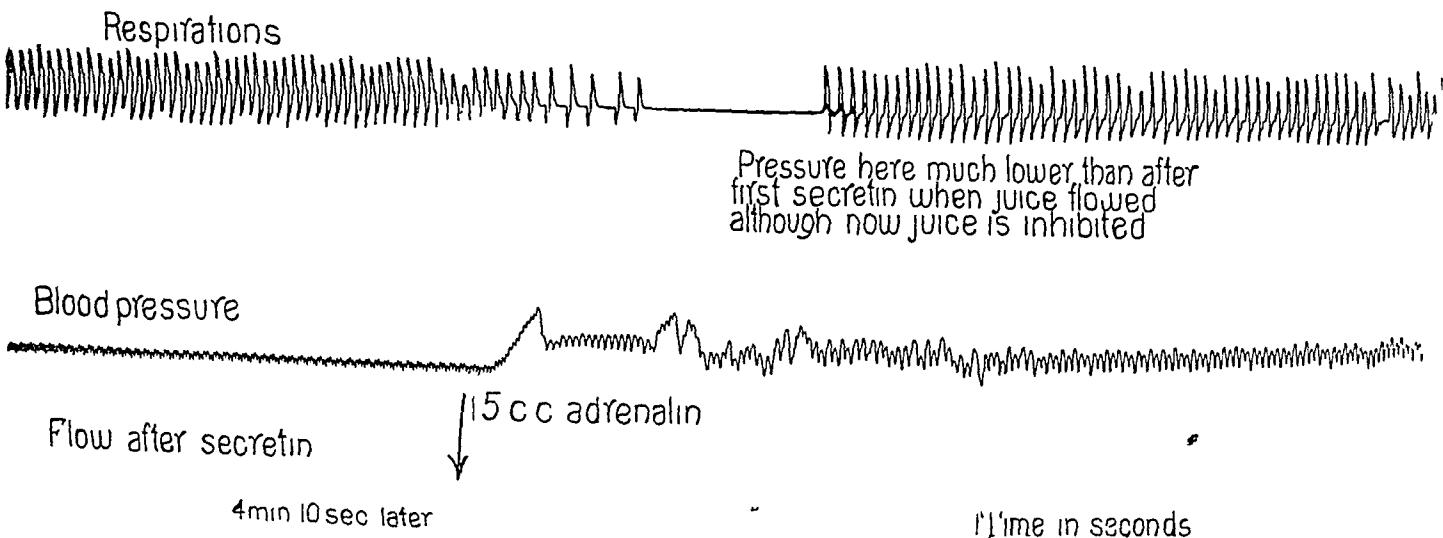


Fig 2.—Tracing, made April 27, 1909, showing inhibition

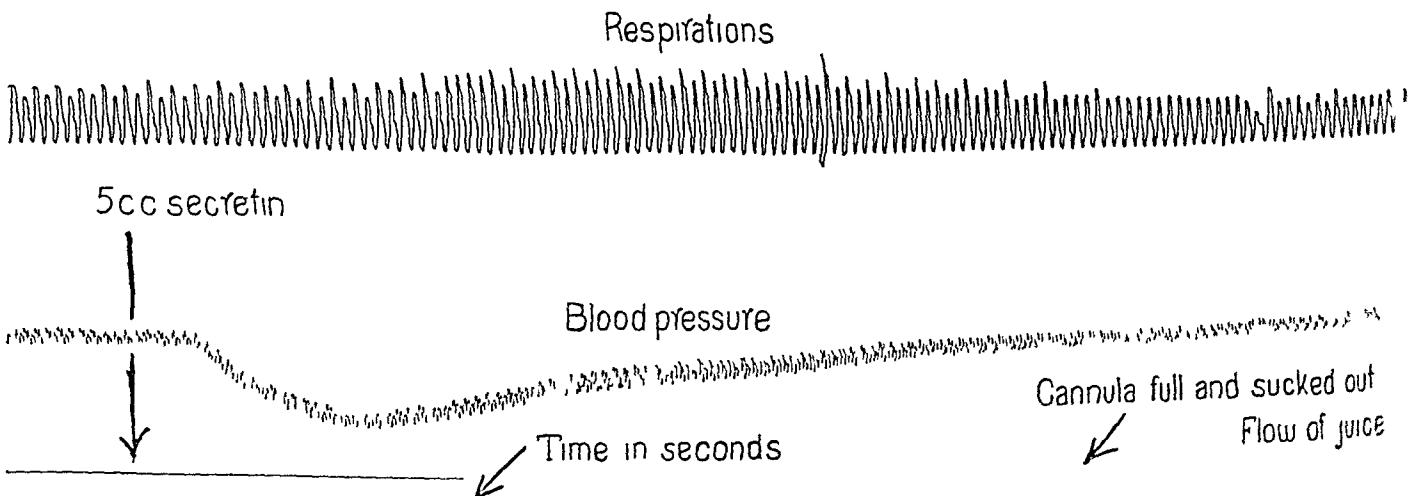
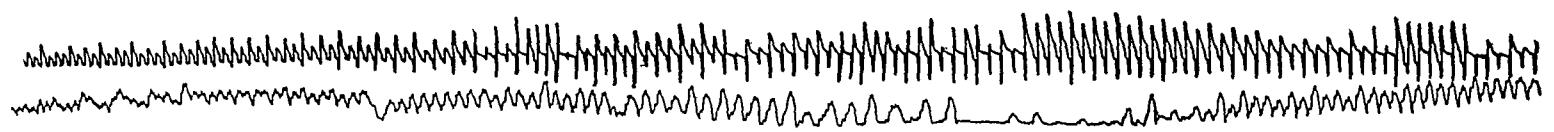
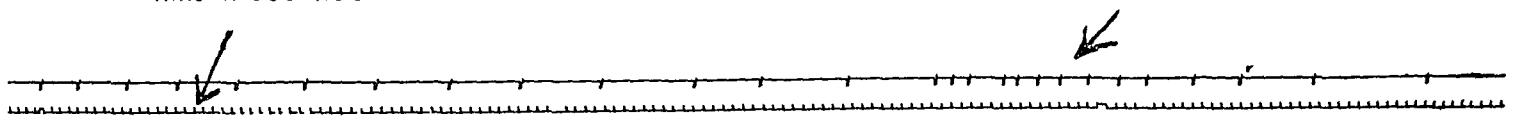


Fig 3.—Tracing made March 7, 1909, showing



Time in seconds

Fairly active flow



tion with disproportionately high rise of blood-pressure in normal dog

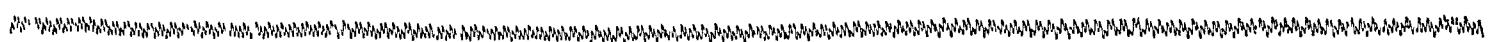
spirations



Normal respirations



sproportionately slight rise of blood-pressure



Cannula full again



tial response to secretin in dog with marked tetany

TRACING (SEE FIG 1), MADE APRIL 27, 1909, SHOWING RELATIVELY SLIGHT INHIBITION WITH DISPROPORTIONATELY HIGH RISE IN BLOOD PRESSURE IN NORMAL DOG

Interval Since Last Injection		Dosage c c	Blood Pressure		Response
Min	Sec		Mm	Mm	
		5 Secretin	75	46	Slight
5	30	10 Secretin	75	38	Very good
4	50	5 Secretin	80	55	Good
1	30	10 Adrenalin	75	95	Very slight inhibition
8	10	5 Secretin	75	45	Very slight
4		5 Secretin	75	45	Very slight
3		10 Secretin	74	23	Slight
2	10	10 Adrenalin	50	107	Inhibition
4	20	10 Secretin	42	23	Slight
3	50	5 Adrenalin	40	50	No inhibition
4	25	10 Secretin	58	26	Slight
1	50	10 Adrenalin	34	34	No inhibition
1	20	10 Adrenalin	42	80	Inhibition
16	20	10 Secretin	60	30	Good
1	45	5 Adrenalin	30	120	Slight inhibition
5	45	10 Secretin	85	40	Very Slight
10	55	10 Secretin	30	16	Slight

TRACING (SEE FIG 2), MADE APRIL 27, 1909 SHOWING INHIBITION WITH DISPROPORTIONATELY SLIGHT RISE OF BLOOD PRESSURE

Interval Since Last Injection		Dosage c c	Blood Pressure		Response
Min	Sec		Mm	Mm	
		5 Secretin	72	42	Very good
5	30	5 Secretin	68	30	Very good
	55	5 Adrenalin	50	142	Inhibition
5		5 Secretin	72	55	None
4	20	5 Secretin	63	44	Very slight
5	55	5 Secretin	43	20	Slight
8		5 Secretin	50	35	Good
4	10	5 Adrenalin	48	52	Inhibition

TRACING (SEE FIG. 3), MADE MARCH 7, 1909, SHOWING VERY GOOD INITIAL RESPONSE TO SECRETIN IN DOG WITH MARKED TETANY

Interval Since Last Injection		Dosage c.c.	Blood-Pressure		Response
Min	Sec		Mm	Mm	
		5 Secretin	50	20	Very good
12	40	5 Secretin	54	23	Very good
1	15	5 Adrenalin	40	90	Inhibition
6		5 Secretin	88	75	Slight
13	45	5 Secretin	58	25	Very good
1	40	5 Adrenalin	45	92	Inhibition
7		5 Secretin	85	60	Good
11	30	5 Secretin	50	28	Very good
1	50	5 Adrenalin	40	80	Inhibition
14		5 Secretin	60	33	Very slight
13	30	5 Secretin	40	22	Very good
10		5 Secretin	45	20	Very good
1	55	5 Adrenalin	40	72	Inhibition
6	50	5 Secretin	75	55	Slight
14	30	5 Secretin	40	25	Good

TRACING (SEE FIG. 6), MADE JAN 22, 1909, SHOWING FAILURE OF HIGH BLOOD-PRESSURE, FOLLOWING ADRENALIN, TO INHIBIT FLOW IN NORMAL DOG

Interval Since Last Injection		Dosage c.c.	Blood Pressure		Response
Min	Sec		Mm	Mm	
		10 Secretin	50	18	Very good
1	20	10 Adrenalin	50	110	No inhibition
5	20	10 Adrenalin	52	95	Followed at once by the next injection
		50	10 Secretin	90	Very good
9	25	10 Secretin	52	16	Very good
		40	3 Adrenalin	22	Inhibition
3	50	10 Secretin	100	30	Good
5	40	3 Adrenalin	40	102	Inhibition
1	40	10 Secretin	85	75	None

secretion by adrenalin, it becomes pertinent and interesting to inquire whether, under similar circumstances of thyroidectomy and parathyroidectomy, adrenalin still exercises its customary influence on the external activity of the pancreas.

To this end, therefore, we experimented on a total number of thirty-six dogs, removing from all of them the thyroids and parathyroids. A

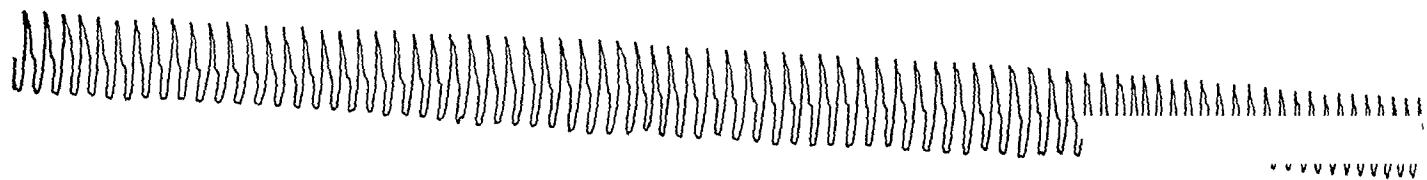
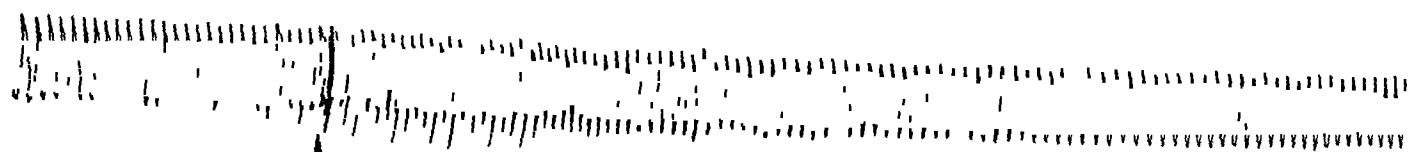


Fig 4.—Tracing (same experiment as Figure 3), made one hour, sixteen minutes later than in record shown in Fig 3 Fourteen minutes



Drum stopped for a few seconds

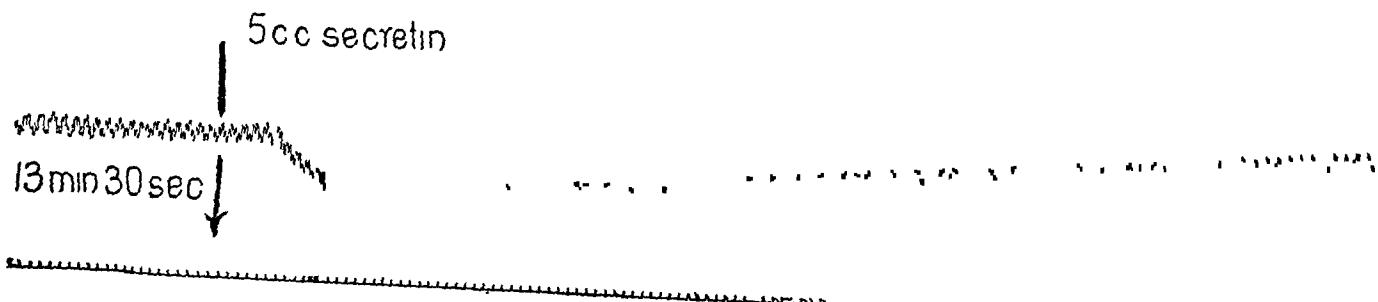


Fig 5.—Tracing (same experiment as Figures 3 and 4), made thirteen minutes later. Several more responses followed

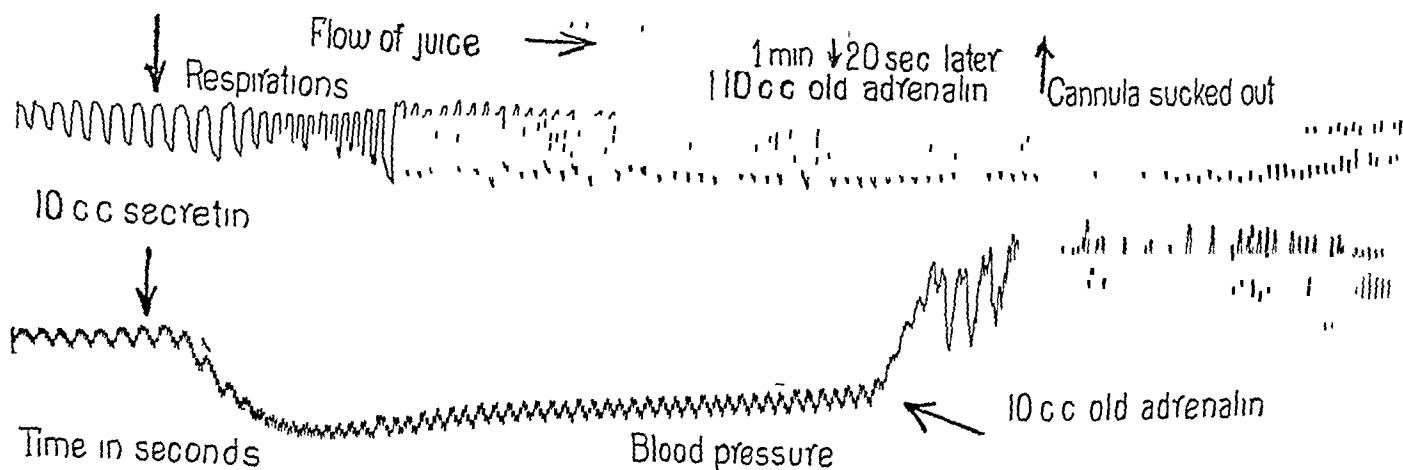
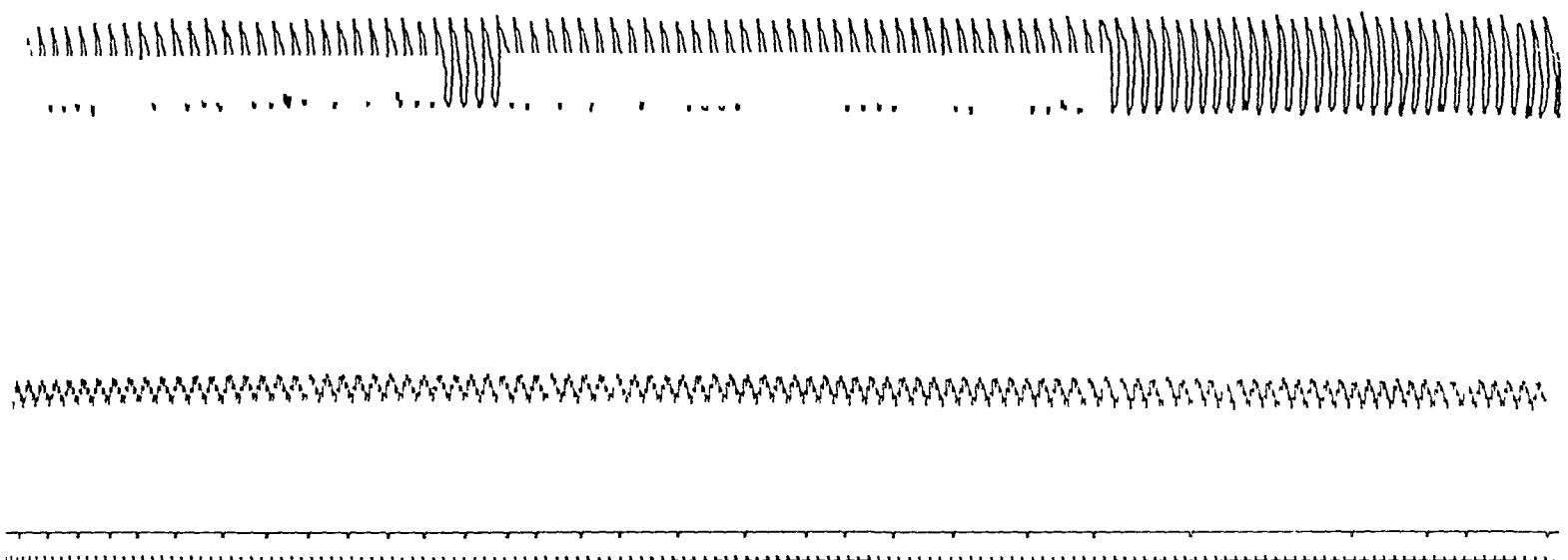
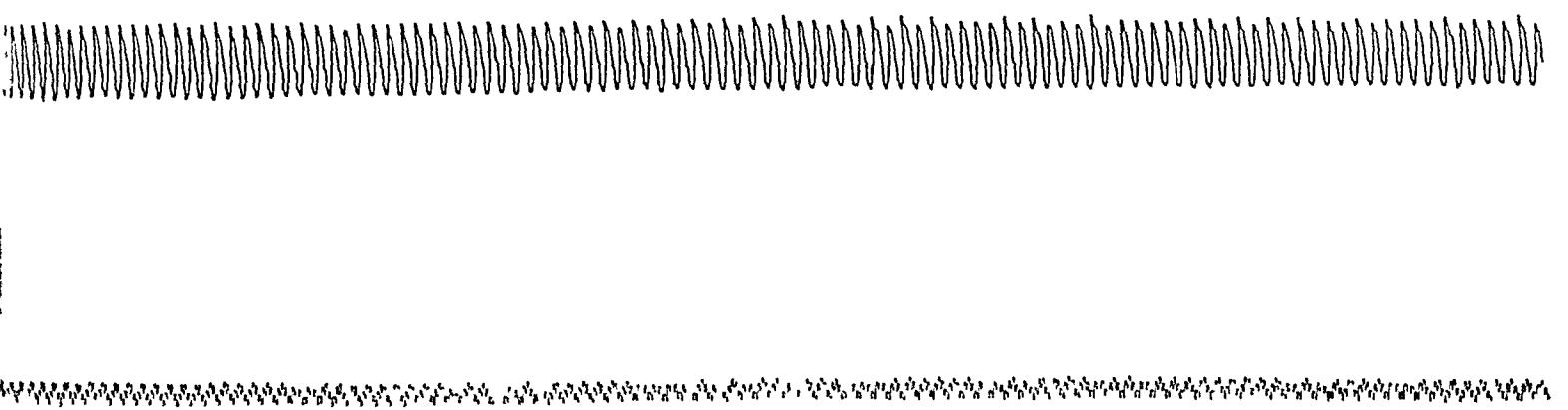


Fig 6.—Tracing, made Jan 22, 1909, showing failure of



and thirty-six seconds later, relative inhibition after adrenalin, though blood pressure  
to this record adrenalin gave marked inhibition No dosage intervened



Cannula emptied

irty seconds later than Figure 4 This shows that the pancreas still responds well  
blood pressure about as in last

Cannula full again

Cannula full

blood pressure following adrenalin, to inhibit flow in normal dog

certain proportion of these dogs failed to develop tetany, as has been the experience of all operators, and of those which did develop it a certain number died shortly after beginning anesthetization

Our aim was to use for investigation those dogs which showed the first signs of developing tetany, as indicating thereby that the thyroid and the parathyroids had both been removed. But it was often impossible to operate at the time of election, as many of our animals when used were more advanced in the disease and represented, in fact, all stages of its progress, even that prior to the onset of evident muscular weakness. Where the dogs seemed as yet perfectly well after the operation, several were taken, on the principle that even in the absence of proof that all the parathyroids had been removed it was safe to assume that two out of three dogs so treated—the usual proportion—would develop tetany later and were at this time, consequently, the subject of some disturbance following the thyroidectomy and parathyroidectomy.

When, therefore, we were satisfied, as above, that the thyroid and parathyroids had been entirely removed, a cannula was placed in the duct, and the usual tracings were established to record blood-pressure and respiration.

Secretin in varying amounts was then given intravenously and attempts were made to inhibit by adrenalin the pancreatic flow thus caused. In the light of some of the work reported by others we looked for some lowered inhibition from it, but none appeared. In a long series of dogs we could not convince ourselves that, in the absence of the thyroid and parathyroids, stimulation of the pancreas by secretin was any more active than in health or that inhibition from adrenalin was one whit less marked or less definite. In short, the pancreas responded to stimulation as it does normally, and the relation of adrenalin toward the external secretion of the pancreas seemed about as in health. It will be observed that the attempt was made in all our dogs to remove both thyroids and parathyroids and that some of the animals were subsequently subjected to investigation before the appearance of tetany, as before mentioned. It therefore seems probable that we have also included in our series cases where inadvertently the thyroids alone were removed, that is, where enough parathyroid tissue still remained to maintain health. One such dog is alive and well at present writing, six months after the operation. This being so, it seems that we might also state that adrenalin behaves toward the pancreas after thyroidectomy alone as it does in health, but, as we have made no systematic efforts toward that end, such a conclusion can hardly be postulated, however likely.

We have been engaged on some other problems along these same general lines of interglandular co-relation which have led to suggestive and interesting results. We reported these in part when we first read this paper, but, as we are now concerned with their further amplification, it seems best to incorporate these fuller observations in a separate contribution which we hope to make in the near future.

#### CONCLUSIONS

1 The inhibition of pancreatic activity by adrenalin and pituitary extract is independent of the systemic blood-pressure, as shown by its persistence when the blood-pressure is much below normal and by other evidence.

2 The inhibition by extracts of pituitary and suprarenal bodies also occurs when the pancreas is stimulated by its normal excitant, hydrochloric acid, in the duodenum.

3 In dogs rendered diabetic by extirpation of the pancreas, the mucosa of the duodenum remains abundant, in striking contrast to the emaciation of the other tissues, and acid extracts of the mucosa are as active as, if not more so than, those from normal animals.

4 Studies of the activity of pancreatic secretion (when excited by secretin) and of the inhibition of pancreatic flow by adrenalin in thyro-parathyroidectomized dogs have indicated no clear departure from the normal in this regard. This is probably also true of dogs the subject thyroidectomy alone.

The accompanying records are illustrative of the conditions described in the text. Corresponding to each record is a legend of the same date and number, the abbreviated history of the case from which the sections are taken for reproduction. The abbreviations are almost self-explanatory, the first column indicates the interval elapsing since the last injection, the second column indicates the nature and amount of injection, the third and fourth columns indicate the blood-pressure immediately before the injection and a short time after it, the last column denotes the nature or failure of response. The blood-pressure as here recorded does not always represent the true blood-pressure, as unfortunately we did not set the base line at zero in our earlier experiments, but it is probably fairly near the truth and is at all events invariably constant for any one experiment.

In conclusion we wish to express to Dr. Edward T. Reichert our appreciation of his kindness and of the facilities he has placed at our command.

We wish also to acknowledge a very real obligation to Dr. David L. Edsall for his constant interest in the work and the uniform readiness with assistance and advice, which have encouraged us to pursue this investigation.

# THE BLOOD-PRESSURE IN EPIDEMIC CEREBROSPINAL MENINGITIS

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PHILADELPHIA

Increased intracranial pressure is a phenomenon which is considered to be nearly always associated with acute inflammation of the cerebrospinal meninges. This phenomenon is caused by the calling into the rigid bony-walled space within the skull and vertebral column of large amounts of inflammatory exudate, while the absorption is, according to Krehl,<sup>1</sup> at the same time probably decreased. This heightened pressure has been regarded generally as one of the most potent factors in causing the symptoms of acute meningitis, and relief has been sought through lowering the pressure by withdrawing the cerebrospinal fluid by means of lumbar puncture.

On account of the intimate relation that has been shown by Cushing<sup>2</sup> and others to exist between intracranial and blood-pressure, it was thought that a series of observations on the blood-pressure in cases of epidemic cerebrospinal meningitis would prove of interest, especially when the effect of withdrawal of the cerebrospinal fluid was considered. Cushing's experiments showed that when the intracranial tension was raised by means of salt solution forced into the subdural space of the cranium and vertebral column the blood-pressure rose, and he reached the conclusion that an increase of intracranial tension occasions a rise of blood-pressure which tends to find a level slightly above that of the pressure exerted against the medulla. His experiments have been recently fully confirmed by Eyster, Burrows and Essick.<sup>3</sup>

During the present study an attempt has been made to answer the following questions. If a heightened intracranial tension exists is it sufficient to cause a rise of blood-pressure? If a heightened blood-pressure exists does the withdrawal of the cerebrospinal fluid cause a fall of blood-pressure by lowering the intracranial tension?

1 Krehl Pathologische Physiologie, Leipsic, 1907, Ed 5, p 556

2 Cushing Concerning a Definite Regulatory Mechanism of the Vasomotor Center Which Controls Blood-Pressure During Cerebral Compression, Bull Johns Hopkins Hosp., 1901, xii, 290

3 Eyster, Burrows and Essick Studies in Intracranial Pressure, Jour Exper Med., 1909, xi, 489

Aside from the bearing which blood-pressure observations may have on these questions, it seems desirable to report the following study, because, according to Janeway,<sup>4</sup> no clinical observations on blood-pressure in connection with inflammatory lesions of the central nervous system have been published.

Observations were made in 26 cases of epidemic cerebrospinal meningitis which occurred in the wards of the Pennsylvania Hospital. From these 336 blood-pressure estimations were made and charted. The effect on the blood-pressure of withdrawal of the cerebrospinal fluid by lumbar puncture was studied 39 times in these cases and 7 times in other conditions. The blood-pressure was estimated as a routine daily, except when lumbar puncture was performed, when it was taken directly before and after the procedure and again a few hours later. The Stanton instrument with a 10 cm arm-band was used, and only the systolic pressure determined, the method of palpation being employed.

The first question to be considered is whether in these cases of meningitis there was evidence of heightened cerebrospinal pressure. The tension of the cerebrospinal fluid as measured by a manometer after lumbar puncture is the most direct method of answering this question. This procedure was done 16 times with the following result:

Above 500 mm	3 times
400-500 mm	5 times
300-400 mm	4 times
200-300 mm	2 times
150-200 mm	2 times

In one case, that of a child of 10 years, the fluid rose to height of 710 mm. Of the two cases in which it rose not above 200 mm one was that of a child of 10 years, the fluid from whom rose 180 mm in the manometer, while from the other patient, aged 24, it rose 150 mm. Normally the spinal fluid rises to a height of about 120 mm in a manometer above the point of puncture in adults, but the normal level, of course, varies considerably. Oppenheim<sup>5</sup> considers a rise of above 150 mm as abnormal, while Seifert and Muller<sup>6</sup> place 200 mm as the upper normal limit. Comparing these figures with the ones obtained in our cases, it is seen that as far as the question has been investigated a heightened intracranial pressure was almost constantly present.

4 Janeway The Clinical Study of Blood-Pressure, New York, 1904, p 253

5 Oppenheim Diseases of the Nervous System, Philadelphia, 1904, Second American Edition

6 Seifert and Muller Taschenbuch der medicinisch-klinischen Diagnostik, Wiesbaden, 1909, Ed 13, p 170

An analysis of the blood-pressure curves in the 26 cases of meningitis fails to show any constant relation to the heightened intracranial pressure. The accompanying table gives the highest and lowest systolic pressure observed in each case, the findings in the 13 patients who were over 14 years of age are given first and the children in the second part of the table.

HIGHEST AND LOWEST SYSTOLIC PRESSURE (MM Hg) IN 26 CASES OF MENINGITIS

No	Age	High- est Pres- sure	Day of Dis- ease	Low- est Pres- sure	Result	ADULTS	
							Remarks
1	31	158	11	155	Death	Moribund while in hospital	
2	45	153	20	108	Recovery	High pressure late in disease	
3	18	148	4	103	Recovery	High at onset	Low during convalescence
4	44	145	3	70	Death	Terminal fall of pressure	
5	24	130	9	95	Death	High pressure when under ethyl chlorid general anesthesia	
6	42	125	2	100	Recovery	Low during convalescence	
7	31	125	2	75	Death	Terminal fall of pressure	
8	38	120	8	90	Death	Terminal fall of pressure	
9	15	120	4	75	Death	Terminal fall	Patient moribund while in hospital
10	36	115	3	75	Death	Moribund while in hospital	
11	56	110	6	100	Death	Moribund while in hospital	
12	16	110	4	108	Recovery	Only two observations made	
13	56	105	1	80	Death	Moribund while in hospital	
CHILDREN							
1	10	135	45	95	Death	Typical rise late in the disease	
2	12	125	6	90	Recovery	Highest at onset and irregular during convalescence	
3	8	125	34	82	Death	Rise of pressure accompanying exacerbation symptoms	
4	12	118	23	85	Recovery	Rise accompanying exacerbation subnormal during convalescence	
5	13	118	4	90	Death	High at onset and just before terminal drop	
6	6	115	18	95	Recovery	Highest after recovery	
7	8	112	5	90	Recovery	Slight even elevation	
8	6	110	3, 21	80	Recovery	Low when worse, irregular without relation to symptoms	
9	6	110	15	80	Recovery	High when worse, irregular with striking relation to symptoms	
10	9	108	6	80	Recovery	No great variations	
11	12	107	21	70	Recovery	High when worse, subnormal during convalescence	
12	6	95	6, 21	78	Death	Highest early and again just before terminal drop	
13	8	92	11	72	Recovery	Even low pressure	

In the table it is seen that in 4 adults the blood-pressure rose to a height of 145 mm Hg or higher, and that in 6 children of between 6 and 13 years it rose to 115 mm Hg or higher. While it is, of course, difficult to say what the normal blood-pressure in each individual is, there is at times certainly an increased blood-pressure in meningitis, a fact which seems somewhat noteworthy when compared to that found in other infectious diseases. The question has been discussed quite thoroughly by Weigert,<sup>7</sup> both from his own work and from an extensive review of that of others, he concludes that in infectious diseases there is a lowered blood-pressure except in the eruptive stages of the exanthemata and perhaps in the early stages of other infectious diseases, such as typhoid fever, diphtheria and pneumonia. Weigert emphasizes the fact that it is difficult to determine the correct normal and to rule out psychic influences.

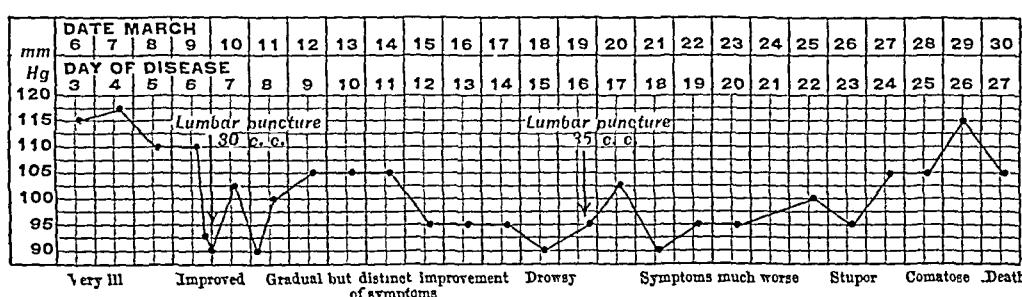


Chart 1—Case 5 of children's division of table, showing early heightened and late rise of blood-pressure

Striking features of the blood-pressure curves are their lack of uniformity to one another, and the great irregularity of the individual curves. The highest blood-pressures were encountered in two stages of the disease, early with the severe symptoms of onset, and later with the preterminal symptoms, before the final failure of the circulation appeared. In some very severe cases in which the patients lived but a few days after the onset, the early severe symptoms represent the preterminal stage, and then it is possible that no blood-pressure records were taken before the failure of circulation had set in. This may be the cause of the low pressures observed in Cases 9, 10, 11 and 13 in the adult division of the table. The marked irregularity of the individual curves is indicated by the wide range between the highest and the lowest systolic pressures observed in many of the cases. A case showing both the early heightened blood-pressure and preterminal rise is seen in Chart 1.

<sup>7</sup> Weigert Ueber das Verhalten des arteriellen Blutdrucks bei den akuten Infektionskrankheiten, Samml Klin Voitr, 1907, xvi, 65

There seemed to be in many of the cases a relationship between the severity of the symptoms and the blood-pressure, the pressure rising when the symptoms, such as fever, headache, delirium, rigidity of the neck and ocular disturbances increased. This relation is seen in Chart 2, in which the high blood-pressure was always obtained when the patient was very ill, while distinct improvement was noted on those days when the lower

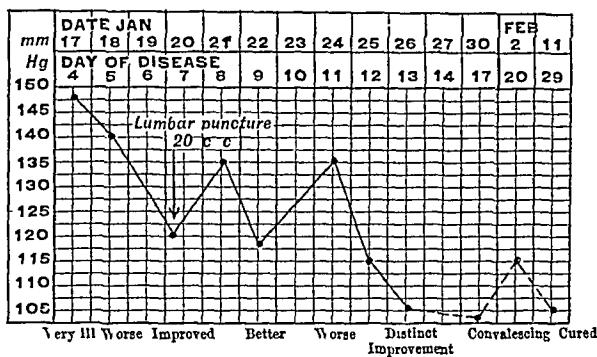


Chart 2.—Systolic blood-pressure, Case 3 of adult division of table, showing relation of blood-pressure to severity of symptoms

blood-pressure was found. In another case in which the patient had a series of alternating good and bad days, the variations in the temperature being especially striking, the blood-pressure chart and temperature chart resembled each other very closely. This relation to symptoms was also

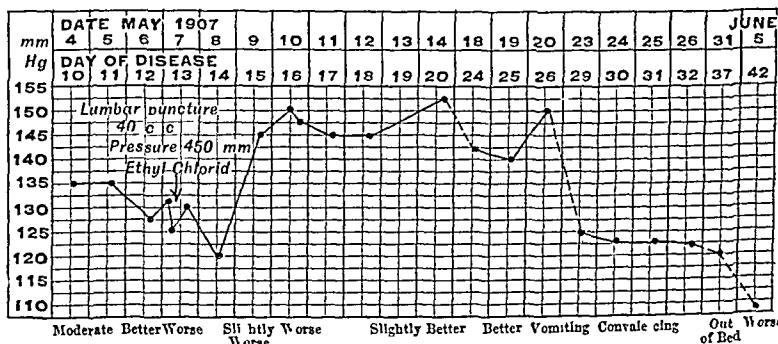


Chart 3.—Systolic blood-pressure, Case 2 of adult division of table, showing exacerbation of symptoms late in the disease, with rise of blood-pressure

seen very plainly in those cases in which the patient became distinctly worse after a period of comparative freedom from symptoms. What might be almost termed a relapse occurred in five of the cases, and in all an accompanying rise in blood-pressure of from 15 to 35 mm Hg occurred. This occurrence is illustrated in Chart 3.

Although it must be borne in mind that the changes in blood pressure in epidemic cerebrospinal meningitis are not great, there is a distinct tendency toward a heightened blood-pressure during the early acute stage and again later in the disease. This tendency is made more striking when the behavior in other infectious diseases is considered.

In endeavoring to determine whether this tendency toward a heightened blood-pressure bears any relation to the increased intracranial tension, the question must be considered whether the withdrawal of the cerebrospinal fluid lowers the blood-pressure. In the series of 39 lumbar punctures in meningitis cases, by which from 0 to 55 cc of fluid (with an average of 32 cc) were withdrawn, the effect was not constant. An average reduction of 10 mm Hg blood-pressure took place in 23 cases, an average rise of 7 mm. in 11 cases, and 5 cases showed no change immediately after the lumbar puncture. In 9 cases ethyl chlorid was given as a general anesthetic during the operation, but this seemed to play no rôle in changing the blood-pressure. In 6 cases the blood-pressure after lumbar puncture was lower than before by 20 mm Hg or more, while in 8 cases it was higher than before the procedure by 5 mm Hg or more. The amount of fluid withdrawn averaged 23 cc in those cases showing a fall of blood-pressure, while in those cases showing a rise of blood-pressure the withdrawn fluid averaged 37 cc. There is no apparent relation between the day of disease on which the lumbar puncture was done and the result on the blood-pressure, nor does the state of the blood-pressure before the procedure or the initial tension of the spinal fluid seem to determine whether the withdrawal of fluid will cause a rise or fall. It is noticed, however, that all patients showing a rise of blood-pressure synchronous with the lumbar puncture are children from 6 to 13 years old. In 6 cases in which fall of blood-pressure occurred immediately, a secondary rise occurred in twenty-four hours, which caused the blood-pressure to exceed its initial level.

It is seen that the blood-pressure is frequently lower after lumbar puncture than before it, but that this is not a constant phenomenon, and bears no apparent relation to the amount of fluid withdrawn, to whether the fluid is withdrawn early or late in the disease, to the initial blood-pressure, or to the initial intracranial tension. It was only in children that a distinct rise of blood-pressure occurred synchronously with the lumbar puncture. Frequently large amounts of cerebrospinal fluid were withdrawn without causing any appreciable effect on the apparently heightened blood-pressure. From these facts the conclusion seems justified that heightened blood-pressure which is frequently seen in epidemic

cerebrospinal meningitis is probably not usually due, at least directly, to the increased intracranial tension

That too much emphasis should not, however, be put on the effect of lumbar puncture in reaching the foregoing conclusion is seen when two cases of cerebral hemorrhage in which lumbar puncture was done are considered. In both cases there was an initial spinal fluid pressure of 250 mm of fluid. The withdrawal of 25 c.c. in one was accompanied by a rise of 20 mm Hg above the initial blood-pressure of 210 mm Hg, while 30 c.c. of spinal fluid withdrawn from the second patient was accompanied by a fall of 18 mm Hg from the initial pressure of 160 mm. In both these cases the increased intracranial tension was probably the cause of the heightened blood-pressure, and yet the withdrawal of the cerebrospinal fluid did not affect the blood-pressure constantly.

The other cases, not epidemic meningitis, in which blood-pressure records were made before and after lumbar puncture, were 3 cases of tuberculous meningitis and one of probable cerebral concussion. In all the blood-pressure was low and in none was it appreciably affected by the withdrawal of from 5 to 65 c.c. of spinal fluid.

Regarded from another point of view, that of the amount of increase of the intracranial tension in meningitis, it seems likely that the heightened blood-pressure when present is due to some other cause than that already discussed. Cushing found that the systemic blood-pressure was not materially affected until the pressure on the vasomotor centers of the medulla approached the level of the cerebral blood-pressure, which, he showed, is for the dog about 150 mm Hg. If such a pressure existed in the subdural space in man, the cerebrospinal fluid should rise very much higher than it usually did in the manometer attached to the lumbar puncture needle. In a case reported by Cushing,<sup>8</sup> in which there was no elevation of the blood-pressure, a blood-clot of 100 c.c. was removed at operation. Here the intracranial pressure was very probably raised to a point above that which occurs in most cases of meningitis.

From a consideration of these facts and from the analysis of the blood-pressure findings in the cases of meningitis here presented, no conclusive evidence is obtained which would justify the assumption that the heightened blood-pressure of meningitis is due to the existing increased intracranial pressure.

When other causes are looked for, a number of factors must be considered. Muscular movements which accompany delirium may have

<sup>8</sup> Cushing. The Blood-Pressure Relation of Acute Cerebral Compression, Illustrated by Cases of Cerebral Hemorrhage. Am Jour Med Sc., 1903, clxv, June.

played a rôle in some cases. The elevation of the blood-pressure may mean that the circulation is endeavoring to meet the extra demands made on it by the fever. There may have been a reflex stimulation of the blood-pressure-raising mechanism of the body by irritation of the central nervous system, or less directly through pain. In a personal communication Dr Theodore Janeway has expressed his opinion that this rise of blood-pressure early in the disease is probably one more of the irritative phenomena, analogous to the slow vagus pulse which often exists, the photophobia, auditory hyperesthesia, delirium, etc. He believes also that reflex peripheral sensory stimulation, especially on the post-spinal nerve roots, must be considered as a possible cause of the rise. What the causes of the blood-pressure changes in meningitis are it is difficult to say, but it is certain that the blood-pressure seems to be nearly always well maintained or heightened as long as the patient remains severely ill, showing that there is no marked relaxation of the vasomotor system. Moreover,

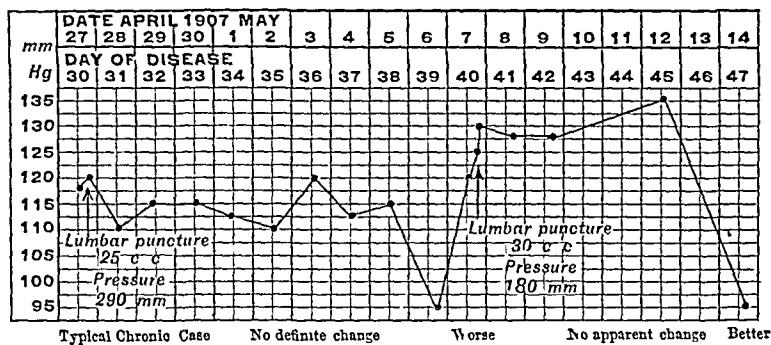


Chart 4.—Systolic blood-pressure, Case 1 of children's division of table, showing marked rise late in disease.

the heart muscle, as a rule, does not become so weakened that it is unable to maintain the pressure until the terminal stage. It seems likely that irritation of the central nervous system plays an important part in the abnormal rise of blood-pressure. Except in the terminal stage when circulatory failure was present, the lowest blood-pressure is seen during convalescence, here, as in other acute infections, it is not infrequently subnormal.

As a possible explanation of the high blood-pressure occurring late in meningitis, especially when the disease appears to take on a chronic phase, the occurrence of internal hydrocephalus or pyohydrocephalus must be considered. Such an occurrence may have been the cause of the rise seen in Chart 4, which occurred in a typical chronic case on the fortieth day of disease. Cushing mentions such a condition as a cause of heightened intracranial tension, and asserts that he has relieved the symptoms and

the congestion of the eyegrounds in a case of pneumococcus meningitis by tapping the ventricles. In this case an acute pyohydrocephalus occurred as the result of obstruction of the foramina of the fourth ventricle. Unfortunately, but one of the fatal cases of our series came to autopsy, and the post-mortem findings throw no light on the condition of the blood-pressure.

#### CONCLUSIONS

Heightened intracranial tension appears to be an almost constant phenomenon in epidemic cerebrospinal meningitis.

Heightened blood-pressure of a moderate degree is not infrequently seen in the early acute stage of the disease when exacerbations of symptoms occur, late in the disease, or when the malady takes on a chronic aspect.

The blood-pressure seems to bear some relation to the severity of the disease, being higher when the symptoms are severe, and low during convalescence.

The withdrawal of cerebrospinal fluid by lumbar puncture has no constant effect on the blood-pressure, although there is usually a fall of blood-pressure synchronous with this procedure.

This series of observations affords no definite evidence that heightened intracranial tension causes an increased blood-pressure in meningitis, unless it is late in the disease, when internal hydrocephalus may develop as a result of blocking of the foramina of the fourth ventricle.

My thanks are due to Drs Morris J Lewis, Arthur V Meigs, and J C Wilson, in whose services at the Pennsylvania Hospital these cases occurred, for putting the material at my disposal.

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## POSTURAL OR ORTHOSTATIC ALBUMINURIA

### A CRITICAL SUMMARY OF THE LITERATURE

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Following Richard Bright's observation, in 1827, of the direct association of albuminuria with pathological changes in the kidneys, the medical profession showed a natural tendency to regard the presence of albumin in the urine as a positive sign of nephritis. It was not long after Bright's discovery, however, that cases began to appear in which examination of the urine showed albumin to be present without any evidences of ill health in the patient and without the fatal outcome commonly associated with nephritis. Such observations have steadily increased in number, so that for some time past there has been an increasing tendency toward the belief that albumin in the urine is not necessarily an indication of serious pathological change in the kidney.

This tendency to regard the presence of albumin as of not very serious moment has led to the adoption of numerous terms to define the condition, such as "functional albuminuria," "albuminuria in the apparently healthy," "intermittent albuminuria," "cyclic albuminuria," "albuminuria of adolescents," "physiological albuminuria," "orthostatic albuminuria," etc. For practical convenience I shall divide the papers to be considered into three groups or periods, the first of which extends roughly up to 1887 and ends with a paper published by Dubreuilh, "A Critical Review of Periodic Intermittent Albuminuria."<sup>1</sup>

#### FIRST PERIOD

Leube<sup>2</sup> was the first to investigate carefully the urine of presumably healthy men. He studied the urine of 119 soldiers in the morning just after they arose from bed, and found albumin in the urine of 42 per cent. The urine of the same soldiers in the afternoon, after several hours of marching, showed albumin in 16 per cent, thus 12 per cent of these soldiers had albuminuria subsequent to prolonged exercise. In all of these cases, the amount of albumin was very slight, never exceeding one gram per liter. As a result of these observations, Leube classified all kidneys as impermeable, semipermeable, or permeable, and located the

1 Dubreuilh Rev de méd, 1887, vii, 678

2 Leube Virchow's Arch f path Anat, 1878, lxxii, 145

permeability in the glomerulus Capitan<sup>3</sup> found albumin in 44 out of 100 soldiers, and in 38 out of 92 children, all in good health. In a thesis published in 1883, Chateaubourg<sup>4</sup> gave the results of numerous studies on soldiers and other subjects at different times of the day and under different circumstances. These results are collected in Table 1.

TABLE 1—RESULTS OF CHATEAUBOURG'S URINARY STUDIES

Cases		Traces of Albumin	Albumin Above 0.03 Gm % Per Liter
Resting	120	76	41
Muscular fatigue after exercise	242	87	66
Mental exertion, school boys, age 16-20	50	92	77
During digestion	94	82	53
After cold baths	53	100	90

The difference in the results obtained by these and subsequent observers may perhaps be explained by the reagents employed, thus, Senator and Posner believe that with sufficiently delicate methods albumin may be found in all normal urines.<sup>5</sup> But, putting aside such cases as the latter, in which the amount of albumin is exceedingly small, there are unquestionably individuals who without any indication of impairment in their general health present an albuminuria which may be easily diagnosed by the coagulation of the protein in the presence of acid. Such cases have been described variously under the names "albuminuria without renal lesion," "albuminuria in the apparently healthy," "albuminuria of puberty," etc. According to some observers, this is nothing but an exaggeration of a normal condition, while others believe that albuminuria invariably indicates a pathological condition of the kidneys. Johnson,<sup>6</sup> for instance, believed that it represents a latent nephritis, and Gardner,<sup>7</sup> on the other hand, has compared the condition to cardiac murmurs, which persist throughout life without other evidences of disease, or to those cases which show localized pulmonary induration, but which never develop acute symptoms of tuberculosis.

Ultzmann<sup>8</sup> was among the first to observe albuminuria in the healthy. In 1870 he detected albuminuria in the urine of eight young girls, who were apparently healthy and strong. The specific gravity of the urine was increased, but neither casts nor red blood cells were ever found. The

3 Capitan Thesis, Paris, 1883 (cited by Dubreuilh)

4 Chateaubourg Thesis, Paris, 1883 (cited by Dubreuilh)

5 Senator Deutsch med Wchnschr., 1904, xxx, 1833

6 Johnson Brit Med Jour., 1889, i, 225

7 Gardner Brit Med Jour., 1884, i, 369

8 Ultzmann Wien med Presse, 1870, xi, 81

sediment frequently showed urates and calcium oxalate crystals. In 1873, in a discussion before the Royal Medical and Chirurgical Society of London, Sir William Gull<sup>9</sup> stated that "boys when they reach the age of puberty are pale and weak, and the urine is frequently albuminous." The first work of importance, however, on this subject was presented by Moxon<sup>10</sup> in 1878. He noted that in young men of delicate complexion, albumin was often found in the day urine. As a result of this paper, the English journals published numerous articles on periodic albuminuria by Rooke,<sup>11</sup> Fergusson,<sup>12</sup> Dukes,<sup>13</sup> Saundby,<sup>14</sup> Yeo<sup>15</sup> and others. In Germany, there appeared the observations of Edlefsen,<sup>16</sup> of Furbringer,<sup>17</sup> and of Bull.<sup>18</sup> The last-mentioned observer followed the case of a young physician, who had daily albuminuria lasting over two years. Munn,<sup>19</sup> an insurance examiner in New York, found albuminuria in twenty-four persons of various ages, who were apparently perfectly healthy, and whose urine showed albumin in the afternoon, but was entirely free during the night. Macacceci<sup>20</sup> emphasized the influence of violent exercise. Kinnicutt<sup>21</sup> also noted intermittent albuminuria in a young man. The latter observer was not able to determine any periodicity, but the character of the urine, its acidity, specific gravity, and the presence of calcium oxalate crystals makes it closely analogous to the type of periodic intermittent albuminuria. The above papers have been collected in a résumé by Lepine, published in the *Revue de médecine*, in 1882. In 1884 Rendall<sup>22</sup> published a thesis in which many observations were given to show that albuminuria was intimately connected with the digestive processes. Pavy, on the contrary, at the meeting of the British Medical Association at Cardiff in 1885,<sup>23</sup> insisted on the importance of the upright position, and excluded entirely the influence of digestion. Pavy's position has subsequently been completely justified.<sup>24</sup> Teissier, in a paper read before

9 Gull Brit Med Jour, 1873, 1, 675

10 Moxon Guy's Hosp Rep, 1878, xxiii, 233

11 Rooke Brit Med Jour, 1878, ii, 596

12 Fergusson Brit Med Jour, 1878, ii, 627

13 Dukes Brit Med Jour, 1878, ii, 794

14 Saundby Brit Med Jour, 1879, 1, 699

15 Yeo Brit Med Jour, 1878, ii, 627

16 Edlefsen Mittl f d Ver Schleswig-Holsteiner Aerzte, 1879, viii, 21

17 Furbringer Ztschr f klin Med, 1880, 1, 340

18 Bull Berl klin Wechschr, 1886, xxiii, 717

19 Munn Med Rec, 1879, 1, 297

20 Macacceci (cited by Dubreuilh)

21 Kinnicutt Arch Med, 1882, viii, 58

22 Rendall Thesis, Paris, 1883

23 Pavy Lancet, London, 1886, 1, 437

24 Sollmann and McComb Jour Exper Med, 1898, iii, 137 Mendel and Hooker Jour Exper Med, 1901, v, 647

the National Society of Medicine at Lyons in the same year,<sup>25</sup> believed that he was able to show that such albuminuria is nothing but the result of abnormal metabolic processes, resulting from general nutritional disturbances

This albuminuria may be present without nephritis, and in people without serious disease, and under various circumstances. It is possible, therefore, according to Dubreuilh, to distinguish three types 1, transitory albuminuria, acute or accidental, 2, chronic albuminuria, without any distinct periodicity, 3, periodic intermittent albuminuria, the cyclic albuminuria of Pavy. The third type is the one which particularly interests us.

#### ETIOLOGY

Sex plays an important part. Thus, in fifty-five cases observed by Dubreuilh, forty-nine occurred in men and six in women. The age is also important. It is most frequently seen during adolescence and in young adults. In 34 cases studies by Dubreuilh, there were 4 boys and 3 girls under 15 years, 14 boys and 2 girls between 16 and 20 years, 7 men between 20 and 25 years, 6 men between 26 and 30 years, and 3 men above 30 years. The age limit cannot be strictly defined, but it is evident from these figures that it is more common about the twenty-first year.

According to the observations of Moxon, functional albuminuria is often present in several members of the same family. He cites several cases of this kind. They generally present the following characteristics:

The subject is listless, and toward evening, he perhaps takes himself to a couch in a languid way. He complains of a headache, and he looks very anemic and gray and sunken about the eyes. He sleeps too much and arises unrefreshed, and is too ready for rest during the working hours. He is usually little disposed to avail himself of cheerful company, but is apt to be content with his state in all these rather unsatisfactory particulars.

According to Teissier, periodic albuminuria is frequently observed in the children of gouty and rheumatic parents, and they are themselves liable to a gouty tendency.

#### URINARY SYMPTOMS

The amount of urine secreted is usually a little less than normal, but in rare cases it may be augmented. The specific gravity is usually equal to, or slightly greater than, normal, and varies generally between 1.020 and 1.030. The color of the urine is normal in the majority of cases. The acidity is generally above normal, and is accompanied by the presence

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25 Teissier Lyon Méd., 1887, liv, 363

of uric acid and calcium oxalate crystals Clark<sup>26</sup> believes that there is an association between the albumin and the oxalate crystals, and he has found that if the cases are treated for oxaluria, the albumin will disappear Jones<sup>27</sup> says that Yale medical students used to eat the stalk of common rhubarb in order to secure calcium oxalate crystals for study which frequently resulted in backache, an irritable bladder and albuminuria Teissier observed numerous granular plaques having the appearance of spontaneously coagulated albumin He also noted a delicate, metallic, bluish tint on the surface, and found that the urine showed a striking tendency to adhere to the glass, giving an opalescent appearance to the surface

The albumin is not very abundant in these cases, never exceeding one gram per liter The heat-acid test is usually sufficient to show the presence of albumin According to Jaccoud<sup>28</sup> and Maguire,<sup>29</sup> the protein present is, in the majority of cases, globulin The latter observed globulin in three typical cases Peptone is also occasionally found

#### PERIODICITY

This form of albuminuria, the cyclic albuminuria of Pavy, is characterized by both its intermittence and its periodicity The night urine is practically always free from albumin, while that secreted during the day invariably shows, at one time or another, albumin in considerable amounts The albumin usually disappears quickly when the subject lies down Cooke followed the case of a young girl for a long period He never observed albumin in the urine collected after she lay down This patient was kept in bed three weeks, during which time albumin never appeared On the first day, however, that the patient was allowed to get up albumin promptly made its appearance Pavy reports similar cases, and believes that for each case there is a particular time of day when the albumin is sure to be present This last observer has never been able to find that food or cold baths have any influence on the appearance of the phenomenon Rendall and also Dukes, however, reported cases in which food seemed to play a very important part Such patients, after rest in bed and a milk diet, did not exhibit albuminuria when they were up and about until a mixed diet was allowed, when the albumin promptly made its appearance

26 Clark Brit Med Jour, 1884, 11, 312

27 Jones Lancet, London, 1886, 1, 432

28 Jaccoud Clin Méd de la Pitié, 1884-85 (cited by Dubreuilh)

29 Maguire Lancet, London, 1886, 1, 1106

Albuminuria in general seems to be very sensitive to cold, although occasionally little or no effect is evident. In some cases, the emotions seem to play an important part, thus Furbringer, Lépine and Clarke report cases in which emotional excitement has been a predisposing cause. The albuminuria appears each day with the same characteristics. The periodicity may, however, not be a daily occurrence. Thus Rosenbach<sup>30</sup> has observed in the case of a generally healthy individual that albuminuria appeared accompanied by headache, loss of appetite, insomnia, etc. The albuminuria in this case lasted from twenty-four to thirty-six hours. The left heart was hypertrophied, and the arterial pressure increased. Teissier has seen the cyclic character of the albuminuria very much altered as the result of exercise. Klemperer<sup>31</sup> reports the case of a student, 23 years old, who, as the result of a severe indigestion, had albuminuria which cleared up when the digestion returned to normal.

#### GENERAL SYMPTOMS AND INCIDENTAL DISTURBANCES

These patients usually show no systemic disturbances, although they are, in general, below par in health, as is evident from Moxon's description given above. They are usually described as being of delicate health, they sometimes present the characteristics of a lymphatic temperament, and frequently evidence nervousness. They are usually pale and anemic, and the young girls are often chlorotic. They present sensations of lassitude and marked languor, as emphasized by Gull in 1873, and subsequently by numerous observers. Palpitation of the heart is a frequent symptom, but without hypertrophy, and the pulse is usually soft. Digestive troubles are usually slight, but sometimes dyspepsia is present (Moxon). Vomiting and dilatation of the stomach (Teissier) have been noted. The tongue is often coated and edema of the eyelids, as observed by Fergusson and Dukes, is not uncommon. Languor, headache and coated tongue constitute an important symptomatology, according to the English observers. Teissier has noted the coincidence of disturbances of the skin (erythema, eczema and urticaria). He has also determined, in the albuminuria cycle, the following phases which occur in the course of the day: (1) elimination of an exaggerated amount of coloring matter, (2) albuminuria, (3) elimination of an exaggerated amount of urine, (4) elimination of an exaggerated amount of urea.

Ralfe<sup>32</sup> noted the frequent coincidence of simple, chronic albuminuria with paroxysmal hemoglobinuria. Several cases came under his observa-

30 Rosenbach Ztschr f klin Med, 1883, vi, 240

31 Klemperer Ztschr f klin Med, 1887, xii, 177

32 Ralfe Lancet, London, 1886, ii, 764

tion which he believed could be intimately associated with the hemoglobinuria Ralfe, on the basis of the experiments of Noel Paton, believes that the liver is the site of the normal destruction of red blood cells If, for any reason, this function of the liver is exaggerated under pathological conditions, or as a result of intoxication, the urinary pigments are increased, and if this process goes on far enough, albuminuria results

According to Ralfe, we have the following schema indicating the relationship between functional albuminuria and hemoglobinuria

Ordinary hemolysis	(Urinary pigment, urea)	Normal urine
Active hemolysis	(Increase of urinary pigment, increase of urea)	Urine of digestion
Increased hemolysis	(Increase of urinary pigment, appearance of bile pigment, increase of urea, albumin in urine)	Functional albuminuria
Extraordinary hemolysis	(Hemoglobin in urine, increase of urinary and bile pigments, increase of urea, albumin in urine)	Hemoglobinuria

It is impossible to determine the duration of the type of albuminuria under discussion In some cases it lasts a few months, but in others it may continue for two or even eight years In general, the prognosis is serious, although not necessarily fatal

Edlefsen is inclined to believe, in accordance with the work of Runeberg,<sup>33</sup> that as a result of exercise, an unusual amount of blood is diverted to the muscular system, which results in a fall of blood-pressure in the kidney, with a consequent albuminuria Such a mechanical theory, however, fails to account for cases to be mentioned later in which the vertical position with muscular exertion excluded was sufficient to produce an albuminuria and in which muscular exertion in the horizontal position was without effect

The theory that it is due to digestive disturbances, advanced by Rendall, is unsatisfactory, because it is impossible to find a direct relationship between the appearance of albumin and the time of meals The effect of cold is, in certain cases, very striking, but it does not apply generally The same may be said of the idea that emotional states bring about the condition

#### SECOND PERIOD

The second period in the development of our subject may be conveniently defined as extending from 1887 until 1904, ending with the

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<sup>33</sup> Runeberg (*Ztschr f physiol Chem*, 1882, vi, 508) has shown that protein filters through animal membrane more rapidly with low than with high pressure

thesis of Guilblain<sup>34</sup> in France, and the work of Edel<sup>35</sup> in Germany. This second period is characterized by the development of scientific interest, and a strong effort to define the etiology of albuminuria by means other than simple clinical observation. Pavy had suggested the name of "cyclic albuminuria." In 1887 Stirling<sup>36</sup> in England proposed the name of "postural," and in 1899 in France, Teissier<sup>37</sup> proposed the name "orthostatic albuminuria," which terms more correctly define the phenomenon under discussion.

Postural or orthostatic albuminuria is most likely to occur between the ages of 16 and 22. Thus Dukes<sup>38</sup> observed between 200 and 300 cases at Rugby. It was formerly thought that the phenomenon was more frequent in boys than in girls. The more recent work has tended to show, however, that sex is of no importance as an etiological factor. In the majority of cases, occurring as they do at the age of puberty, the albuminuria has been associated with the sex function. Masturbation was known to be practiced by many patients. Thus Stirling<sup>39</sup> says that of 37 boys who masturbated, 14 had albuminuria. This author quotes Dickinson as saying, "Most, not all, cases masturbate," and again quotes Dukes, "I do not think masturbation is concerned in it." Stirling is of the opinion that at the age when most cases occur, the sexual functions are rapidly developing, and the nervous mechanism concerned is consequently in an unstable condition. According to Stirling, it is hard to say whether this produces a reflex hyperemia of the kidney, or more probably, a disturbance of the vasomotor system, but he believes that in any case the effect would be much the same. Any cause which would produce this effect might be liable at the same time to produce albuminuria, and therefore albuminuria might be regarded as the result of a local as well as a general deficiency in vascular tone. Dukes and others have suggested that the development of the vascular system at the age of puberty may be an important factor. It is, of course, probable that infectious diseases, such as scarlet fever, which are likely to occur at this time in a child's development, may also play a part. This possibility has led Guilblain to differentiate essential orthostatic albuminuria to cover the cases in which no infections can be found predisposing to the condition. Schaps<sup>40</sup>

34 Guilblain Thesis, Paris, 1903

35 Edel Munchen med Wehnschr., 1901, xlvi, 1833, Deutsch med Wehnschr., 1903, xxix, 639

36 Stirling Brit Med Jour., 1887, ii, 1157

37 Teissier Semaine Méd., 1899, xix, 425

38 Dukes Brit Med Jour., 1889, i, 625

39 Stirling Brit Med Jour., 1889, i, 807

40 Schaps Arch f Kinderh., 1903, xxxv, 41

observes that girls are affected four times as commonly as boys, and is inclined to explain this relationship on Rokitansky's observation that developmental anomalies are more common in the vascular system of girls than of boys. Of 35 subjects, 20 showed more or less pathological hearts. These troubles were not, however, organic, but rather due to the hypertrophy and dilatation, coincident to growth described by Germain Séé.

Admitting that posture plays an important part in the causation of albuminuria, numerous observers have sought an explanation in the accompanying muscular exertion. Experimental observation has not, however, confirmed this idea. Thus Guilblain found that muscular exertion in the horizontal position did not cause albumin to appear, and that if the subject was maintained in the upright position passively, albuminuria promptly occurred, and finally, that light exercise tended to decrease rather than to increase the amount of albumin secreted. Osswald<sup>41</sup> also observed that the horizontal position of the body caused the albumin to decrease or disappear in from twenty to sixty minutes. Under such conditions, muscular exertion had no effect on the albuminuria. The same thing was observed when the subject was maintained in the sitting position.

Considerable attention has been paid to the influence of the position of the body on the secretory activity of the kidney. Linossier and Lemoine<sup>42</sup> studied the amount of water, urea, phosphates and sodium chloride secreted, standing and lying, in normal individuals, and in those with orthostatic albuminuria. Their results are given in Table 2.

TABLE 2—RATIO OF VARIOUS SUBSTANCES IN URINE, SUBJECT STANDING AND LYING

	Normal	Albuminuric
Water	82 100	64 100
Urea	131	82
P <sub>2</sub> O <sub>5</sub>	112	80
NaCl	104	63

They are inclined to infer from these figures that orthostatic albuminuria borders on the pathological. Achard<sup>43</sup> and Merklen and Claude,<sup>44</sup> using Koranyi's quotient  $\Delta/\text{NaCl}$ , were unable to find, however, any abnormality in the excretion of urine in subjects with orthostatic albuminuria.

41 Osswald Ztschr f klin Med, 1894, xxvi, 73

42 Linossier and Lemoine Compt rend Soc de biol, 1903, lv, 466

43 Achard Compt rend Soc méd d hôp, 1900, June 22

44 Merklen and Claude Compt rend Soc méd d hôp, 1900, July 27

Blood-pressure has been considered as an important causative factor in albuminuria. Dukes<sup>45</sup> quotes Benke as saying

The development of the heart at puberty is to be regarded as a very important phase in the development in regard both to the physical and pathological occurrences of this period of life. The large arterial vessels attain their relatively narrowest condition at the time of puberty, hence with the increased development of the heart, with relatively narrow arteries, we must get increased arterial tension.<sup>46</sup>

According to this theory, Dukes presupposed a renal hyperemia, which, in the majority of cases, is just held in check, and believed that he was able to determine increased arterial tension in all of his cases. Craig,<sup>47</sup> in England, seems to have been the first to suggest definitely that albuminuria is present as the result of low arterial tension, he cites cases of anemia and hemorrhage in which albuminuria is likely to be present. Furthermore, he states that he was able to cause functional albuminuria to disappear by raising the blood-pressure. Herringham<sup>48</sup> describes a patient as follows "He was a lean, pale boy with a feeble circulation and soft pulse."

Guilblain emphasizes the importance of distinguishing essential orthostatic albuminuria from the intermittent albuminuria of chronic nephritis, from digestive or dyspeptic albuminuria, from pretuberculous albuminuria described by Teissier,<sup>49</sup> from cyclic albuminuria (Pavy), from fatigue or physiological albuminuria, from the albuminuria accompanying hemoglobinuria, and from metabolic albuminuria.

It is not uncommon to observe an intermittence in the albuminuria present with chronic nephritis. It can, however, in the majority of cases be readily distinguished from the true orthostatic albuminuria. Digestive or dyspeptic albuminuria can be readily distinguished by its association with meals or with digestive upsets. The pretuberculous albuminuria of Teissier invariably exhibits albuminuria in the early morning hours. The cyclic albuminuria of Pavy may or may not fall into the class under discussion. Fatigue or physiological albuminuria has been carefully studied by Lommel<sup>50</sup> and by von Leube.<sup>51</sup> Lommel found among 587 apprentices, aged 14 to 18 years, that albuminuria was present in 18.9 of the cases. Von Leube states that this

45 Dukes Brit Med Jour, 1878, II, 794

46 This assumption is not in accord with the observation that there is a continuous elevation of arterial (systolic) blood-pressure from the sixth to the eighteenth year. See Potain, La pression artérielle de l'homme, Paris, 1902, p 102.

47 Craig Brit Med Jour, 1886, I, 333

48 Herringham Brit Med Jour, 1891, I, 218

49 Teissier Congres de Méd, Lyon, 1894, L Savy, Lyon, 1895

50 Lommel Deutsch Arch f klin Med, 1903, lxxviii, 541

51 Von Leube Deutsch med Wochenschr (Vereins-Beilage), 1902, xxviii, 309

form of albuminuria is present in from 20 to 50 per cent of cases observed. It may, of course, be brought on as the result of fatigue, and may or may not include the cases of orthostatic albuminuria. Metabolic albuminuria has been emphasized by Charrin<sup>52</sup>. Charrin observed that the blood-pressure, freezing-point of the urine, toxicity of the urine, temperature of the urine, the absorption of oxygen, and the rectal temperature, follow in general the output of albumin. He maintains that all these phenomena are the result of metabolism, and hence that albuminuria may be regarded as a nutritional disease. The albuminuria coincident to hemoglobinuria has been already considered in connection with the work of Ralfe.

Throughout the period at present under discussion, observers were divided between the views that all albuminuria is pathological, and that some cases are harmless. The majority, however, are inclined to the latter view. Casts in the urine might be regarded as of important pathological moment. Most observers, however, have been unable to observe their presence, although some have found hyaline casts. Huger<sup>53</sup> observed two cases. In both he was able to find hyaline casts, and believes that a careful examination of the urine will, in all cases, reveal their presence.

The prognosis for orthostatic albuminuria is, according to Guiblain, excellent. We thus see a distinct change in the point of view over that held at the time Dubreuilh prepared his paper. The presence of albuminuria in such a large percentage of cases has made the subject of great interest from the point of view of life-insurance. Therefore, the discussion of this aspect of the subject has become very general, and we find that writers are inclined to a broader interpretation of albuminuria than formerly. Shepherd,<sup>54</sup> in 1888, reported the results from 35,000 examinations of urine. He noted that the brain-workers showed a larger percentage of albuminuria than the muscle-workers, that in the large majority of cases albuminuria is not associated with renal disease, and that in the matter of life-insurance, albuminuria should be looked on as a symptom only, and acceptance or rejection of the risk should depend on the gravity of the case. Tyson, in a paper read before the Association of American Physicians in 1888,<sup>55</sup> came to a similar conclusion. This paper was discussed editorially in the *British Medical Journal* the following year.<sup>56</sup> The writer admitted the difficulty of examination in

52 Charrin Jour de Physiol et path gén, 1901, III, 58

53 Huger Bull Johns Hopkins Hosp, 1902, XIII, 75

54 Shepherd Boston Med and Surg Jour, 1888, cxviii, 575

55 Tyson Tr Assn Am Physicians, 1888, 171

56 Editorial Brit Med Jour, 1889, I, 26

such cases, but concluded that albuminuria, as such, was not a sufficient reason to refuse insurance.

The fact that variation in arterial tension was not sufficient to explain the presence of albumin in the urine, together with the difficulty of accounting for the phenomenon on the ground of a venous stasis, since albumin is not present in such cases in the sitting posture, led to the suggestion that a movable kidney might be the proper explanation. This idea was first suggested by Sutherland<sup>57</sup> in America in 1903, and was advanced by Guiblain at about the same time. This belief has not, however, received wide acceptance, although one case has been recently reported by Blum,<sup>58</sup> in which it was found that an aberrant renal artery was pressed on by the ureter, thus producing albuminuria.

Throughout this period (1887 to 1903), numerous observers suggested the idea that vasomotor instability might be the etiological factor in question, but Edel was the first to bring forward definite evidence substantiating this conception. In his first paper, published in 1901, he noted that diuretics caused the albumin to disappear from the urine. Hot baths also decreased the amount of albumin, under which condition he observed that the skin was flushed, the pulse fuller and faster, and that the amount of albumin was inversely related to the amount of urine. Pribram<sup>59</sup> had also observed fifteen cases of orthostatic albuminuria in which the specific gravity always varied directly as the albumin present. Edel noted also that moderate exercise without fatigue improved the strength of the pulse by stimulating the heart action and decreased the amount of albumin, causing also an increase in the amount of urine secreted. He therefore suggested as a rational therapeutic measure that the heart should be strengthened by careful exercise, that in no case should the subject be kept in bed, and that rich diuretic food should be indulged in. In his second paper published in 1903, he reported observations on the blood-pressure. In such cases, the effect of warm baths on normal individuals was to cause a slight fall in blood-pressure—10 mm during the bath, which rose 25 mm after the bath. Albuminurics, however, failed to show this rise in pressure after the bath, and had sensations of relaxation and fatigue instead of feeling refreshed, as was the case in normal individuals. As the result of cold sponges, the blood-pressure of albuminurics was not as responsive as in the case of controls, but tended to remain constant, or sometimes to fall, while in the normal cases there was usually a rise. Exercise (climbing

57 Sutherland Am Jour Med Sc, 1903, cxvi, 289

58 Blum Wien med Wochenschr, 1908, xxI, 503

59 Pribram Centralbl f inn Med, 1889, II, 482

stairs) produced a much less pronounced effect on the blood-pressure of albuminurics than on that of normal individuals, as shown by his figures here given (Table 3)

TABLE 3—EFFECT OF EXERCISE ON BLOOD-PRESSURE OF NORMAL AND ALBUMINURIC INDIVIDUALS

	Before	Just After	2 Min After	20 Min After
Normal	136	205	181	136
Abnormal—Morning		+ 37	(not stated)	(still more)
Afternoon		+ 17	+ 16	0

Just after bicycle-riding the blood-pressure was high. Fifteen minutes after riding, however, the blood-pressure was low again and albumin made its appearance. When normal individuals changed from the sitting to the standing posture, the blood-pressure rose and seemed to remain elevated, while in the case of albuminurics the blood-pressure did not rise and sometimes fell. From these observations Edel infers that orthostatic albuminuria depends on the inability of the cardiovascular system to respond to ordinary changes. He believes that the heart and vascular system are very important in fatigue, and the fact that subjects suffering with albuminuria are readily fatigued tends strongly to support the belief that the two are intimately associated.

### THIRD PERIOD

The third period in the development of our knowledge of orthostatic albuminuria, extending from 1903 up to the present time (1909), offers only three new suggestions for the etiology that presented by Teissier,<sup>60</sup> implying a developmental defect in the glomerulus,<sup>61</sup> that offered by Erlanger and Hooker,<sup>62</sup> and that of Jehle.<sup>63</sup> Teissier, in a paper published in 1905, is careful to distinguish between true orthostatic albuminuria and mixed albuminuria. The former, he says, is characterized by the juvenile appearance of the patient, a poorly developed vascular system and small heart, low arterial pressure and a subnormal body weight. Such cases may or may not give a history of infection. When the patient changes from the lying to the standing position, albumin promptly makes its appearance in the urine and disappears as quickly when he lies down.

60 Teissier Revue de Med., 1905, xxv, 233

61 This is practically the suggestion of von Leube, but stated with more boldness and decision

62 Erlanger and Hooker Johns Hopkins Hosp Rep., 1904, vii, 145

63 Jehle Munchen Med Wchnschr., 1908, lv, 12

Nervous symptoms are frequently associated. In such cases the amount of albumin excreted varies from 0.5 to 4 gm per liter. The protein is serum albumin. Globulin is only exceptionally present. If any protein is associated with the serum albumin it is practically always nucleo-albumin.<sup>64</sup> In agreement with von Leube, he conceives of permeable, semipermeable and impermeable kidneys, and believes that orthostatic albuminuria falls into the class of semipermeable kidneys, due to a defect in the development of the glomerulus. Jehle observed a case of orthostatic albuminuria, which, however, exhibited casts and blood elements. From the study of this case, he came to the conclusion that the albuminuria was caused by lordosis which resulted in a pressure on either the renal vessels or the ureter. With this conception of the cause of the albuminuria, he favored exercise as a therapeutic agent, because it would strengthen the muscles of the back and thus improve the condition of lordosis and coincidentally the albuminuria. Nothmann<sup>65</sup> has recently confirmed Jehle's observation, that lordosis may be the cause of orthostatic albuminuria. He has succeeded in producing albuminuria by artificially induced lordosis. Observations on the cadaver and on rabbits indicate that curvature of the spine could disturb the normal position of the kidneys to an extent sufficient to explain the disturbances in the circulation, which are evidently responsible for the albuminuria. I shall later on refer to the work of Erlanger and Hooker.

It is interesting to note the effect of athletic exercise on the appearance of albumin. Dunhill and Patterson,<sup>66</sup> in Australia in 1902, and W. Collier,<sup>67</sup> in England in 1907, investigated the urines of boat crews and found that albumin was invariably present after the races.

Rose Bradford, in an address before the British Medical Association in 1907,<sup>68</sup> reached the conclusion that there was no adequate explanation of the phenomenon under discussion, except that of vasomotor insufficiency.

Adam Loeb,<sup>69</sup> in Germany in 1905, studied the behavior of the quotient  $\Delta/\text{NaCl}$  in cases of nephritis, cardiac disease and orthostatic albuminuria. On the theoretical assumption that an increase in the quotient means a decreased flow of blood through the kidneys and a decrease in the quotient means an increased flow of blood through the kidneys, he found that those with orthostatic albuminuria and those

64 This statement has been entirely substantiated by other observers.

65 Nothmann Arch f Kinderheilk., 1909, xlii, 216.

66 Dunhill and Patterson Intercol Med Jour Australasia, 1902, vii, 334.

67 Collier Brit Med Jour, 1907, i, 4.

68 Bradford Brit Med Jour, 1907, i, 725.

69 Loeb Deutsch Arch f klin Med, 1905, lxxviii, 452.

with cardiac disease both showed an increase of  $\Delta/\text{NaCl}$ , together with a lessened excretion of sodium chlorid and water on the patient's assuming the upright position which was accompanied by the appearance of albumin in the urine. These conditions did not hold for nephritis. Philippson,<sup>70</sup> however, has recently been unable to make this sharp distinction. Loeb thus believed that the condition of albuminuria was dependent on the cardiovascular disturbances, probably vasomotor in origin, which found their origin in infectious diseases.

Porges and Pribam<sup>71</sup> and Pelnar<sup>72</sup> studied the effect on the albuminuria of substances which would tend to alter the circulation, such as coffee, strychnin, diuretin, chloral hydrate, morphin, adrenalin, purgatives, severe exercise, etc. No positive results were obtained. Porges and Pribam determined the blood-pressure with Gartner's tonometer. Since they were unable to note any great changes in the arterial pressure, and since venous stasis and movable kidney were excluded, they concluded that the condition must be a result of constrictor spasm of the renal artery.

In 1904 Erlanger and Hooker published an extensive study of blood-pressure in a case of orthostatic albuminuria, using the Erlanger sphygmomanometer.<sup>73</sup> Blood-pressure changes were induced by various physiological procedures, such as muscular exertion, compression of the legs with Crile's pneumatic suit, cold and hot baths, etc. As a result of this investigation, the only factor which was found to vary directly as the appearance of the albumin and inversely as the amount of urine excreted was the pulse-pressure. The pulse-pressure was found to vary in a normal individual in the same direction as in the albuminuric, but not, however, to the same extent. It seems probable, therefore, that the permeability of the kidney of a person suffering with orthostatic albuminuria must be greater than in a normal individual, and that the appearance or non-appearance of albumin is dependent on the nutrition (oxygen supply?) of the organ, brought about by variations in the amplitude of the pulse.<sup>74</sup>

In a paper published by Leonard Williams in 1908,<sup>75</sup> the suggestion is made that orthostatic albuminuria, since it is common in the early

70 Philippson Jahrb f Kindeh, 1906, lxiii, 174

71 Porges and Pribam Deutsch Arch f klin Med, 1907, xc 367

72 Pelnar Centralbl f inn Med, 1905, xxvi, 1025

73 For a description of the instrument see Erlanger, Johns Hopkins Hosp Rep, 1904, xii, 53

74 This may be regarded as a very conservative conclusion, since it fails to take into consideration exercise albuminuria, as well as the peculiar sensitiveness of the normal kidney to interference with its circulation.

75 Williams Clin Jour, 1908, xxxii, 23

years of life, is due to an incomplete functional development of the vasomotor system. He cites the fact that the urine of new-born children almost always contains albumin, which disappears from the urine after the vasomotor system has become adapted to its new requirements.

In 1907 Heubner presented before the Medical Society in Berlin the results of an autopsy on a young girl who had been suffering with orthostatic albuminuria.<sup>76</sup> Only a single minute lesion, 1 by 15 mm in extent, was found in the pole of the right kidney. This is the only case of autopsy found in the literature. Heubner does not believe that the lesion in itself was sufficient to account for the albuminuria present. The child came of a tuberculous family, had had measles and scarlatina and had been operated on for adenoids one year before she came under observation. Her first appearance was in 1903, when she came to the clinic for a cough and a swelling of the neck. The urine at this time was free from albumin. In the following year, May, 1904, the patient returned complaining of headache, as well as the former symptoms. At this time she showed slight edema of the eyelids and feet and exhibited orthostatic albuminuria. In November of the same year her eyesight had become weak, and choked disc was present with attacks of vomiting. A diagnosis of cerebellar tumor with secondary hydrocephalus was made at this time. The albuminuria was more severe, but still orthostatic in type. Early in 1905 the patient was operated on. She died in October of the same year. Throughout the time during which she was under observation no casts were found in the urine.

This report was followed by a lengthy discussion by Senator, Langstein, Baginsky, Furbringer, Hansemann, Orth and others.<sup>77</sup> The consensus of opinion was that the lesion was insufficient to account for the albuminuria observed.

Finally, I should mention the work of Wright and Ross,<sup>78</sup> who have found it possible to cure patients with orthostatic albuminuria by the administration of calcium. They made use of this treatment on the assumption that the albuminuria is the result of an abnormality in the blood. Calcium acts to hasten the coagulation of blood and presumably increases the viscosity. Furthermore, the administration of calcium lactate served, in the hands of these observers, to differentiate renal from non-renal albuminuria, the excretion of albumin in the former not being affected.<sup>79</sup> Teissier's observation of the coincidence of skin troubles in

76 Heubner Berl klin Wehnschr, 1907, xliv, 1

77 Berl klin Wehnschr, 1907, xliv, 61

78 Wright and Ross Lancet, London, 1905, ii, 1164

79 I have been unable to confirm this in a case recently under observation

such cases, and the theory advanced by Ralfe, are of interest in connection with the work of Wright and of Luff<sup>80</sup>. The latter has found, following the suggestions of Wright, that calcium lactate is a very efficient therapeutic agent in persistent cases of chilblains boils associated with cold hands and feet, urticaria, erythema, lichen planus, pruritus, hemoglobinuria, etc., complaints which, he discovered, were, in all his cases, associated with retarded blood-coagulation. No determinations of blood-pressure have been reported for cases such as those described by Wright, and it is not known what effect the calcium has on the physics of the circulation.<sup>81</sup>

Throughout this discussion it must have been evident that the variations in the point of view presented by different observers might be accounted for by variation in the cases observed. There can be no doubt, however, that it is possible for albumin to make its appearance in the urine without the consequent assumption of pathological conditions in the kidneys. We should not be justified, however, in ignoring the opinion of Senator, who has probably given more attention to diseases of the kidney than any man now living, and who has, throughout the years in which albuminuria has been so hotly discussed, maintained unflinchingly his belief that protein in the urine must be regarded as evidence of pathological conditions in the kidney. I quote from a recent address:

With the lapse of time I am only more strongly confirmed in the view, which I expressed years ago, that a slight irritation or inflammatory condition, which may progress toward recovery or toward a diffuse chronic nephritis, is responsible for most, if not all, of the cases of "cyclic" or orthostatic albuminuria.<sup>82</sup>

Of the numerous theories dealing with the causation of orthostatic albuminuria, that of a vasomotor instability stands out prominently to account for the typical cases. The work of Edel, of Loeb, and of Erlanger and Hooker gives direct support to this view. Loeb, Lanossier and Lemoine, and Erlanger and Hooker were able to show that the kidneys in orthostatic albuminuria did not excrete the ordinary urinary constituents normally. Edel reached the conclusion that a low systolic

80 Luff Brit Med Jour, 1909, 1, 261

81 It is of interest in this connection to note that the case observed by Erlanger and Hooker was subject to eczema. The attacks of eczema ceased, however, approximately coincidently with the natural disappearance of the albuminuria.

82 Ich bin somit je langer je mehr in der schon vor Jahren von mir ausgesprochenen ausicht bestarkt worden, dass, wenn nicht allen, so doch den allermeisten Fallen von "cyklischer," namentlich orthostatischer (orthotischer) Albuminurie ein leichter Reiz—oder enzündlicher Zustand in den Nieren zugrunde liegt, welcher in Heilung übergehen, aber auch bis zu einer diffusen chronischen Nephritis sich weiter entwickeln kann. Senator Deutsch med Wchnschr, 1904, xxx, 1833

blood-pressure was an invariable concomitant of albuminuria Erlanger and Hooker were unable to observe any consistent relationship between the appearance of albumin and the systolic or diastolic blood-pressure or the velocity of blood flow in the aorta There was, however, an invariable inverse relationship between the appearance of albumin and the magnitude of the pulse-pressure Since, however, the behavior of the pulse-pressure, under varying conditions, was qualitatively the same in the control and in the albuminuric, no sharp line of demarcation could be drawn The suggestion was tentatively advanced that variations in the magnitude of the pulse-pressure might influence the oxygen supply to the renal epithelium, and so alter its functioning properties In the case under observation, the pulse-pressure was uniformly less than that of the normal individual, and showed, as did the systolic and diastolic blood-pressures, a marked tendency to be less stable This tendency was repeatedly emphasized by attacks of syncope during the periods of observation When we consider the phenomenal sensitiveness of the normal kidneys of animals to the slightest alteration in their blood-supply (momentary clamping of the renal artery or vein, etc), some support is added to the suggestion of a transient nutritional disturbance Definite proof must rest, however, on the successful perfusion of the isolated kidney

Recently I have collaborated in the observation of a second similar case, the results of which have not yet been published It is of interest to state here that this recent work corroborates entirely that done with Dr Erlanger It may be of interest to state also that the patient studied by Erlanger and Hooker has entirely recovered from his albuminuria

That the albumin of orthostatic albuminuria and the post-exercise albuminuria first observed by Dunhill and Patterson may result from the same immediate cause, namely, a decrease of pulse-pressure, is indicated by recent investigations of exercise on the arterial blood-pressure Barach, Boyce and Savage determined the systolic and diastolic pressures in a number of individuals before and after Marathon races<sup>83</sup> In these individuals the urine was normal before the runs After the exertion the urine contained casts, blood, albumin and acetone bodies This change in the urine was accompanied by a marked diminution in the amplitude of the pulse-pressure In this laboratory shorter runs have been observed to result in albuminuria In these cases both systolic and diastolic pressures were greatly increased immediately after the exercise, the systolic the more so that the pulse-pressure was increased This increase gave way at once to a fall of both pressures accompanied by a

<sup>83</sup> Reported before the American Physiological Society, December, 1909

decrease of pulse-pressure Faint traces of albumin were found in the first urines voided after the exercise The albumin increased in amount with the post-exercise fall of pulse-pressure (independent of the changes in systolic and diastolic pressures) and disappeared with the return of this factor to normal It would appear, therefore, that orthostatic albuminuria is not necessarily directly associated with a permanent impairment of renal function

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## PARATYPHOID CHOLECYSTITIS

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The striking similarity which exists between typhoid and paratyphoid fever holds true not only for their mode of onset and clinical manifestations, but also as regards the character of complications encountered. Secondary paratyphoid infections of the bone, joint, testicle, middle ear and bladder have all been reported, while, according to Lorrain Smith,<sup>1</sup> intestinal hemorrhages occur in 5 per cent of all cases.

The frequency of typhoid cholecystitis would, therefore, warrant the expectation of often meeting gall-bladder disease in paratyphoid fever. While this expectation may be warranted, I have been able to collect from the literature only six authentic cases of paratyphoid cholecystitis. Lorey<sup>2</sup> reported a case of paratyphoid cholecystitis, Type B, in 1908, and asserted that he could find in the literature no other cases of that type which were entirely free from objections.

In looking over the records of cultures taken from the last fifty-two cases of gall-bladder operation in the Presbyterian Hospital, I find that I isolated the colon bacillus sixteen times, the streptococcus seven times, *Bacillus pyocyaneus* and the paratyphoid bacillus once each. In the remainder of the cases the cultures were sterile.

Schottmuller<sup>3</sup> was the first to divide paratyphoid bacilli into two groups. This classification was based on definite cultural and biological differences and has received abundant confirmation. Brion and Kayser<sup>4</sup> designated the groups as Type A and Type B, the former turning milk slightly acid, the latter producing a faint alkalinity, and each developing specific immune bodies. Infections with the Type A paratyphoid bacillus are rare, particularly in Germany. In America this type of paratyphoid fever occurs more frequently. Proescher and Roddy<sup>5</sup> have recently

\* From the Pathological Laboratory of the Presbyterian Hospital, New York.

1 Smith Allbutt and Rolleston's System of Medicine, 1, 1157.

2 Lorey Munchen med Wehnschr., 1908, Iv, 15.

3 Schottmuller Ztschr f Hyg u Infektionskr., 1901, xxvi, 368.

4 Brion and Kayser Munchen med Wehnschr., 1902, vlx, 611.

5 Proescher, F., and Roddy, J. A. A Report of Forty Eight New Cases of Paratyphoid Fever (Type A), THE JOURNAL, A. M. A., 1909, lxi, 470.

reported forty-eight cases of Type A infections from the Allegheny General Hospital

The case of paratyphoid cholecystitis which I am about to report falls within the Type A group, and is especially interesting in that the patient gave no history of a previous attack of typhoid or paratyphoid fever. I am indebted to Dr Eliot for permission to use the clinical history.

*Patient*—L C, female, aged 25, married, admitted Nov 23, 1908, to the first surgical division of the Presbyterian Hospital, complaining of abdominal pain, nausea and vomiting. Family history negative. Personal history negative. Measles in childhood. No other acute illness. No history of typhoid or paratyphoid fever.

*Present History*—Two years ago patient was suddenly taken with severe colicky pains in the gall-bladder region. Attack was accompanied with vomiting, fever and slight jaundice. About one year later, patient had another attack similar to the first. Since then she has been subject to frequent attacks. For the last three weeks she has been constantly ill. Pain is very severe, and radiates to back. Nausea, headache and fever are constant.

*Physical Examination*—Patient is fairly well nourished, but looks ill. Chest negative. Abdomen is soft except in the upper right quadrant, where there is some resistance. In the region of the gall-bladder there is a pear-shaped mass, moving with respiration, and slightly tender. Temperature, 101.5, leucocytes, 12,600. Urine shows bile. Clinical diagnosis, cholelithiasis.

*Operation*—On November 25 a cholecystectomy was performed by Dr Eliot. At the operation the omentum was found firmly adherent to the gall-bladder. Wall of gall-bladder was thickened, mucosa was swollen. Gall-bladder contained greenish semiviscid bile, and numberless small stones. The bile ducts were patent. An abscess containing two ounces of pus was found near the foramen of Winslow. Microscopically, the mucous membrane of the gall-bladder was partially absent, and the other coats were densely infiltrated with polymorphonuclear leucocytes and lymphoid cells.

*Bacteriologic Examination*—Smears from the gall-bladder mucosa show many polymorphonuclear leucocytes and small gram-negative bacilli. Plate cultures from the bile, and also from the interior of one of the stones, give a pure growth of an actively motile, gram-negative bacillus. On agar, this organism forms small grayish-white translucent colonies. Litmus milk is acidified, but there is no coagulation after two weeks' growth. Neither blood-serum nor gelatin are liquefied. In Dunham's peptone solution no indol is produced. Broth becomes turbid, but no pellicle is formed. Glucose broth, 1 per cent, is fermented, with the production of a small amount of gas. Saccharose broth is free from gas. In lactose broth there is no gas. In mannite broth there is a small bubble after forty-eight hours. One cubic centimeter of the twenty-four-hour broth culture, when injected intraperitoneally, killed a guinea-pig in less than twenty-four hours. Agglutination tests with the patient's own serum were carried out with a number of organisms. Table 1 shows the results obtained with the various dilutions.

## PARATYPHOID CHOLECYSTITIS

TABLE 1—AGGLUTINATION TESTS, PATIENT'S SERUM AGAINST VARIOUS ORGANISMS \*

Organism	1-10	1-20	1-50	1-100	1-200	1-500	1-1000	1-2000	1-5000
Bacillus from patient	+	+	+	+	+	—	—	—	—
<i>B paratyphosus</i> , Schott-muller A	+	+	+	+	+	—	—	—	—
<i>B paratyphosus</i> , Schott-muller B	+	—	—	—	—	—	—	—	—
<i>B typhosus</i>	—	—	—	—	—	—	—	—	—
<i>B coli communis</i>	—	—	—	—	—	—	—	—	—

\* Readings for the three lowest dilutions taken at end of one half hour, for high dilutions, two hours

The typhoid bacillus was not agglutinated, even by high concentrations of the patient's serum. The colon bacillus was not agglutinated. The patient's own organism was agglutinated up to a dilution of 1/200. Two other strains of paratyphoid bacillus Type A, were agglutinated at a dilution of 1/100, both microscopically and macroscopically. Two strains of *Bacillus paratyphosus*, Type B, showed some clumping at dilutions of 1-10 and 1-20, but many of the organisms retained their motility. With higher dilutions the reaction was entirely negative. On Jan 2, 1910, 1 c.c. of a twenty-four-hour culture of dead bacilli from the patient was injected subcutaneously into a male rabbit. On January 7 it received 0.5 c.c. of a living culture, and increasing doses every five days thereafter. The last two doses were given intravenously. At first the rabbit lost weight, but later he regained a considerable part of it. On Feb 5, 1910, after having received seven injections, the rabbit's serum was tested for agglutinins. Table 2 shows the results obtained.

TABLE 2—AGGLUTINATION TESTS WITH RABBIT'S SERUM \*

Organism	1-10	1-20	1-50	1-100	1-200	1-500	1-1000	1-2000	1-5000	1-10000	1-20000
Bacillus from patient	+	+	+	+	+	+	+	+	+	+	—
<i>B paratyphosus</i> , Schott-muller A	+	+	+	+	+	+	+	+	+	+	—
<i>B paratyphosus</i> , Schott-muller B	+	—	—	—	—	—	—	—	—	—	—
<i>B typhosus</i>	+	+	—	—	—	—	—	—	—	—	—
<i>B coli communis</i>	—	—	—	—	—	—	—	—	—	—	—

\* Readings for the three lowest dilutions taken at the end of one half hour, for remaining dilutions, two hours

The patient's own organism was agglutinated by a 1-5000 dilution of the rabbit's serum, while a stock strain of the paratyphoid bacillus, Type A, was agglutinated by a 1-10000 dilution of the same serum. Neither the patient's serum nor the rabbit's serum had any effect on the paratyphoid bacillus, Type B, the typhoid bacillus, or the *Bacillus coli communis*, except in very low dilutions of the serum. On December 12, seventeen days after the operation, the patient's feces were examined for paratyphoid bacilli. Endo's medium was used for the plates. No paratyphoid bacilli were found.

In the case just described we have the picture of a typical chronic cholecystitis, produced by an organism which corresponds in every way

with Biion and Kayser's Type A of paratyphoid bacillus. This bacillus belongs to a group of pathogenic bacteria, intermediate between the typhoid bacillus and *Bacillus coli communis*, which has attained considerable importance for animal and human pathology. To this group belong Gartner's *Bacillus enteritidis*, the two types of paratyphoid bacillus, *Bacillus typhi murium*, *Bacillus surstifer* and various meat-poisoning bacilli. There has been considerable disagreement among those who have studied these organisms as to whether they could be definitely differentiated. Bonhof,<sup>6</sup> for example, concluded that the bacillus of mouse typhoid, paratyphoid bacillus Type B, and *Bacillus enteritidis* differed in their pathogenicity for the intestines, but could not be distinguished by either cultural, agglutination or bacteriolytic methods. On the other hand, Bock,<sup>7</sup> Kutscher and Meinicke,<sup>8</sup> Trautmann<sup>9</sup> and others, after carrying out elaborate agglutination tests, were able to separate Gartner's bacillus from the rest of the group. Bainbridge,<sup>10</sup> in addition to the agglutination tests, made use of Castellani's "absorption method." By means of this laborious procedure he succeeded not only in separating *Bacillus enteritidis* from the paratyphoid bacillus Type B, and *Bacillus surstifer*, but also in drawing a distinction between the two latter organisms themselves. Bainbridge asserts that the *Bacillus typhi murium* has no existence as a definite type. All of these investigators agree that the paratyphoid bacillus, Type A, stands quite apart from the rest of this group in both cultural and agglutination reactions.

The case which I have reported bears a striking resemblance to the one reported by Blumenthal<sup>11</sup> in 1904. His patient, a woman, 46 years old, gave no history of typhoid or paratyphoid fever. At the operation there were found thirty-six gall-stones, cultures from which gave a pure growth of the paratyphoid bacillus, Type A. The agglutination test was positive at a dilution of one to three hundred.

In 1903 Pratt<sup>12</sup> reported a case of cholelithiasis in a girl, 18 years old, who was operated on four years after an attack of fever diagnosed as typhoid. Cultures from the gall-bladder and from the stones gave a pure growth of the paratyphoid bacillus, Type B. The patient's serum agglutinated her own organism, but had no effect on the typhoid bacillus.

6 Bonhof Arch f Hyg, 1904, 1, 222

7 Bock Arb a d k Gesndhtsamte, 1905, xxiv, 238

8 Kutscher and Meinicke Ztschr f Hyg u Infkr, 1905, lii, 301

9 Trautmann Ztschr f Hyg, 1903, xlvi, 139

10 Bainbridge Jour Path and Bacteriol, 1909, xiii, 443

11 Blumenthal Munchen med Wehnschr, 1904, h, 1641

12 Pratt Boston Med and Surg Jour, 1903, cxlviii, 137

Lorey's<sup>2</sup> case is similar to Pratt's. A young man, 22 years old, giving a history of typhoid fever two years previous to his attacks of gall-stone colic, underwent an operation. Four stones were found in the gall-bladder. Cultures from the gall-bladder mucosa showed a pure growth of the paratyphoid bacillus, Type B. The patient's serum agglutinated his own organism, as did also the serum from two cases of paratyphoid fever.

Evers and Muhlens<sup>13</sup> record the case of a woman, 38 years old, who gave a history of three weeks' illness, characterized chiefly by nausea, vomiting and diarrhea. Two days before the operation she was suddenly taken with colicky pains in the gall-bladder region, and severe icterus developed. There was no history of typhoid or paratyphoid fever. The gall-bladder contained considerable pus and many small stones. A pure culture of the paratyphoid bacillus, Type B, was obtained from the pus. Several strains of this organism were agglutinated at a 1-200 dilution of the patient's serum. The organisms were also found in the feces. It is interesting that another woman in the same pavilion developed gastro-enteritis shortly afterward, and the paratyphoid bacillus, Type B, was isolated from the stools.

Zimmer<sup>14</sup> has recently reported a case of paratyphoid cholecystitis which was diagnosed from a bacteriologic examination of the feces. The paratyphoid bacillus, Type B, was isolated. This organism was agglutinated by the serum from a case of paratyphoid fever, but the patient's serum failed to agglutinate his own organism. There was no surgical or post-mortem examination in this case.

Forster and Kayser<sup>15</sup> examined the bile of 148 cadavers for bacteria, and found the paratyphoid bacillus only once, and that in a case of diabetes mellitus. The gall-bladder contained two stones. The bile gave a pure culture of the paratyphoid bacillus, Type B, but cultures from the interior of the stones were sterile. In this case there was no history of typhoid fever or paratyphoid fever. The identity of the bacillus was established by "the usual cultural and immunity reactions."

In addition to these six cases of paratyphoid cholecystitis, several observers have found paratyphoid bacilli in gall-stones that showed no pathological changes.

Libman,<sup>16</sup> as far back as 1902, isolated the paratyphoid bacillus from the gall-bladder in a paratyphoid fever patient who was operated on for

13 Evers and Muhlens *Deutsch Med - u. ztl Ztschr*, 1909, *xxviii*, 366

14 Zimmer *Mitt d Gesellsch f inn Med u Kinderh in Wien*, 1908, *vii*, 34

15 Forster and Kayser *Munchen med Wochenschr*, 1905, *lii*, 1473

16 Libman *Jour Med Research*, 1902, *viii*, 168

suspected gall-bladder disease. The gall-bladder was distended with thick dark bile which could not be pressed out. After the operation, intense jaundice developed and the patient died on the following day. At the autopsy, however, the gall-bladder and bile ducts showed no changes.

Lucksch<sup>17</sup> has reported a case of paratyphoid fever that came to autopsy. Cultures from the bile showed the organism, but there were no inflammatory changes in the gall-bladder.

The interesting features in connection with my case are the following:

1. The absence of a history of typhoid or paratyphoid fever. Two hypotheses may be advanced in explanation of this. The attack of fever was a very mild one or the case was one of primary paratyphoid infection of the gall-bladder. Muller,<sup>18</sup> Blumenthal,<sup>19</sup> Forster and Kayser,<sup>20</sup> Churchman<sup>21</sup> and others have reported analogous infections with the typhoid bacillus. In the cases of paratyphoid cholecystitis reported by Blumenthal, Evers and Muhlens, and Forster and Kayser, there was no history of any previous attack of fever.

In this connection it is interesting to consider the cases of febrile icterus in which there have been found agglutinins for the typhoid, paratyphoid and other intestinal bacteria. Rostoski,<sup>22</sup> for example, studied forty-one cases of icterus, and found that the serum from almost half of them agglutinated the typhoid bacillus. Some observers, such as Rostoski, and Ludke,<sup>23</sup> believe that the reaction is often due to molecular changes in the blood, but Christian<sup>24</sup> thinks that the phenomenon when actually present is caused by an infection of some part of the biliary tract. Netter and Ribadeau-Dumas<sup>25</sup> have reported sixteen cases of febrile icterus, in fourteen of which the paratyphoid bacillus, Type A, was agglutinated by high dilutions of the patient's serum. Of the two remaining cases, one agglutinated the Type B of paratyphoid bacillus, and the other Gartner's bacillus. These observers consider the paratyphoid bacillus, Type A, the predominant exciting agent in febrile icterus.

2. Another interesting feature of the case which I have just reported was the marked agglutinative power of the patient's serum. In a dilu-

17 Lucksch Centralbl f Bacteriol, 1903, xxiv, Abt I, Orig, 113.

18 Muller Ztschr f Heilk, 1905, vii, 310.

19 Churchman Bull Johns Hopkins Hosp, 1909, xx, 89.

20 Rostoski Sitz-Ber d phys med Gesellsch, Wurzburg, 1904, p 69.

21 Ludke Deutsch Arch f klin Med, 1904, lxxxi, 34.

22 Christian Boston Med and Surg Jour, 1907, clvi, 536.

23 Netter and Ribadeau-Dumas Compt rend Soc de Biol, 1905, lvii, 436.  
450

tion of 1-200 there was complete agglutination of her own organism at the end of one hour. The agglutinations were also specific, the serum having little or no effect on the typhoid or paratyphoid bacillus, Type B, but acting readily on other strains of the A type. The agglutination reactions were also positive and specific in the other cases of paratyphoid cholecystitis, to which I have already referred.

3 One other feature of this case is worthy of mention. No paratyphoid bacilli were found in the feces when it was examined seventeen days after the operation. Unfortunately, no examination was made before the operation or immediately after it. The patient, however, had most probably been a paratyphoid carrier. The cases reported by Lorey, Blumenthal, Zimmer, and Evers and Muhlens all showed paratyphoid bacilli in the feces. In Zimmer's case the diagnosis was made by the positive findings in the feces. Nearly all investigators are agreed that the source of the bacteria in typhoid and paratyphoid carriers is in an infected gall-bladder. That the gall-bladder may act as a reservoir for these organisms is evident from the fact that after removal of the infected viscera the bacilli, as a rule, disappear from the feces. In cases in which they persist after removal of the gall-bladder, an infected common duct is probably the focus from which the bacteria are discharged.

A considerable amount of experimental work has been done in the effort to define clearly the relation of typhoid and paratyphoid fever to the gall-bladder. Blackstein and Welch<sup>24</sup> injected typhoid bacilli intravenously into rabbits, and found that long after the other organs were sterile the gall-bladder contained them in large numbers. In one of their cases typhoid bacilli were found in the gall-bladder one hundred and twenty-eight days after the injection.

Forster and Kayser<sup>25</sup> repeated these experiments, with similar results. They found that the same conditions obtained when the bacilli were injected directly into the gall-bladder.

Dorr<sup>25</sup> carried out some experiments which seemed to show conclusively that the bacilli reach the gall-bladder by way of the blood-stream rather than by means of an ascending infection from the intestine. Dorr employed subcutaneous and intraperitoneal injections of typhoid bacilli, as well as administration by mouth, with negative results. After intravenous injections, however, the gall-bladder contained large numbers of bacilli. Ligation of the cystic duct before the intravenous injection prevented the entrance of the bacilli into the gall-bladder, while ligation

<sup>24</sup> Blackstein and Welch Bull Johns Hop Hosp, 1891, 11, 96, 121

<sup>25</sup> Dorr Centralbl f Bacteriol, etc, 1905, XXXI, Abt I, Orig 624

of the common duct had no such effect Dorr concluded from his experiments that the bacilli were excreted from the circulation by the liver, and then passed into the gall-bladder

Chiarolanza<sup>26</sup> has recently repeated these experiments and demonstrated the presence of typhoid bacilli in the gall-bladder even after the cystic duct was ligated Chiarolanza also found typhoid bacilli in the small intestine after ligation of the common duct

J Koch<sup>27</sup> made a histological study of the gall-bladder in typhoid cholecystitis, and also in animals injected with the typhoid bacillus, and could find small nests of bacilli in the terminal capillary ramifications of the gall-bladder mucosa Some of these nests had already ruptured into the gall-bladder lumen, after producing more or less necrosis of the tissue about them

Chiari's<sup>28</sup> investigations led him to conclusions quite different from those of Koch Chiari isolated the typhoid bacillus from the gall-bladder of seven out of eight cases of typhoid fever that came to autopsy In only two of these cases, however, did the gall-bladder show pathological changes Chiari could find no bacteria or clumps of bacteria in the smaller blood-vessels, and was convinced from his studies that infection, when it did occur, was from within outward

Forster<sup>29</sup> takes the same position He believes that when typhoid or paratyphoid bacilli are taken into the system they pass at once into the circulation and reach a lymph-gland where they multiply This occurs during the period of incubation Later they appear in the circulation, are taken up by the liver and pass into the gall-bladder where they again encounter conditions favorable to multiplication The bacilli pass out from the gall-bladder into the intestine and infect Peyer's patches Working on this theory, Forster tried various methods of flushing out the gall-bladder in typhoid carriers, but this mode of treatment was not efficacious

If the results of Koch and Chiarolanza can be corroborated, we have in them a satisfactory explanation of the mode of infection in typhoid and paratyphoid cholecystitis The demonstration by Chiarolanza of typhoid bacilli in the small intestine, even after ligation of the common duct, suggests that the infection of Peyer's patches is also hematogenous and accomplished by the passage of bacilli from the terminal intestinal

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26 Chiarolanza Ztschr f Hyg u Infektionskr , 1908, lxii, 11

27 Koch, J Ztschr f Hyg u Infektionskr , 1908, lxii, 1

28 Chiari Verhandl d deutsch path Gesellsch , 1907, xi, 143

29 Forster Munchen med Wehnschr , 1908, iv, 1

capillaries into the surrounding tissue, rather than, as Forster contends, a sequel to the infection of the gall-bladder

NOTE—I reported this case of paratyphoid cholecystitis before the New York Pathological Society in December, 1909. In the discussion which followed, Dr Rosensohn reported a case of gall-bladder disease, the patient operated on at the Mt Sinai Hospital. The gall bladder was filled with calculi. Cultures gave a pure growth of the paratyphoid bacillus, Type A, which was agglutinated by a 1-100 dilution of the patient's serum.

41 East Seventieth Street

## A CASE OF INFANTILISM WITH ABSENCE OF THYROID AND TUMOR OF PITUITARY

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AND

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The relation of disease of the hypophysis cerebri to certain forms of gigantism and acromegaly has been long known and widely confirmed clinically. We have only begun to realize the wide variety and numerous combinations of symptoms attributable to pathologic conditions of this little body. Its function is still more or less a mystery, and our idea of its histologic structure has only recently been thoroughly defined. Theories of the effect of its internal secretion on general metabolism have been widely divergent. Clinical observations when correlated with pathologic findings have often seemed to lead to contradictory conclusions. The era of experimentally produced and scientifically controlled lesions has just begun. With the accumulation of data from this source and from the sharpened clinical observations, we may expect soon to have an immense light thrown on this most mysterious of all the mysterious ductless glands. With the hope of adding something toward this result, we wish to report a case which we think presents some new and unusual features.

### REPORT OF CASE

*Personal History*—The patient is a white woman, aged 24, a native of Mississippi and resident there all her life. Her present complaint is of periodic headaches from two weeks to six months apart. She was perfectly well as a child, had measles at 17 years, has never menstruated. She stopped school between 17 and 18 years of age because of her health. Up to that time she had stood well in her classes. Her physician, Dr C R Stingly of Pelahatchie, Miss., writes that she was unusually bright as a child. She has never had ground itch.

*Family History*—Her father and mother are living and well at the ages of 67 and 62, respectively. She is small and slight but fully developed. Two sisters have died, one of typhoid and one of pneumonia. One brother died in childhood. Four brothers are alive and well. One sister is living and has five children. The brothers and sisters were perfectly developed.

*Present Illness*—The patient broke down at school six years ago and had to be sent home because she was nervous. After she came home she soon became well and went to work in the postoffice until June, 1908. In this month she had an attack of fever for three weeks. It was a very slight illness and the fever was always below 102. There was no delirium. Dr Stingly says that "troublesome eye symptoms were the first to attract attention. Then followed headaches, which

became more intense every month" The patient says that these headaches have been frequent during the last three years, but have not occurred more than once a month They would usually last twenty-four hours In November, 1908, she had an attack of headache which lasted from two to three weeks During that time she would forget that she had seen people Sometimes she would seem to be in a deep sleep but she was not entirely unconscious, for she could be aroused but could not always speak Of this attack she does not recall anything It seemed to her that she was off visiting

*Physical Examination*—May 19, 1909 Slight, childish-looking Very intelligent Skin clear Mucous membranes normal Teeth perfect No glandular enlargement Skeleton long, no deformity except that there is a slight evidence of thickening of the costal cartilages No pubic hair No axillary hair Hair of the head is short, but otherwise normal No mammary development The thyroid is not palpable Lungs normal Heart normal, pulse 116, blood pressure low, but not measured Spleen not palpable Liver not palpable No scars on legs Uterus is infantile Ovaries not palpable

#### Measurements

Height, 5 feet 2 inches

Head      Fronto occipital circumference, 20 $\frac{5}{8}$  inches

              Mento-occipital circumference, 22 $\frac{5}{8}$  inches

Chest     At rest, 25 inches

              Full inspiration, 26 $\frac{1}{2}$  inches

              Full expiration, 23 $\frac{1}{2}$  inches

Arm, 12 $\frac{1}{2}$  inches

Forearm, 10 $\frac{5}{8}$  inches

Thumb, from wrist to tip, 4 $\frac{5}{8}$  inches

First finger, from wrist to tip, 6 $\frac{1}{4}$  inches

Second finger, from wrist to tip, 7 inches

Third finger, from wrist to tip, 6 $\frac{5}{8}$  inches

Fourth finger, from wrist to tip, 5 $\frac{7}{8}$  inches

Pelvis    Circumference at anterior superior spines, 26 $\frac{1}{2}$  inches

              Circumference at anterior great trochanters, 27 $\frac{5}{8}$  inches

Thigh     From anterior superior spines to internal condyle, 18 $\frac{3}{4}$  inches

              From symphysis pubis to ground, 33 $\frac{1}{2}$  inches

Blood Examination      Hemoglobin, 85 per cent

              Red blood cells, 4,800,000 to the c mm

              Leucocytes, 6,200 to the c mm

Differential Count

              Polymorphonuclears, 60

              Large lymphocytes, 13

              Small lymphocytes, 18

              Transitionals, 7 7

              Eosinophils, 1 3

Urine    Sp gr., 1006, acid, no albumin, no sugar, no casts

*Neurological Examination*—June 14, 1909 The reflexes showed no abnormalities which could be considered pathological They were all active and equal on the two sides Babinski's sign was absent Sensation to pain and touch, heat and cold, showed no disturbances There was no disturbance in the tuning fork and in the sense of position The patient was perfectly capable of localizing all points correctly There was no ataxia Romberg's sign was absent Examination of the cranial nerves, with the exception of the optic nerve, was negative The hemianoptic pupillary reaction was not present The visual fields

were hemianopic for colors only. The white field showed patches in which there was still capability of distinguishing a moving object.

*Radiographic Examination*—June 15, 1909. Radiographs of long bones (Fig. 2) show lack of ossification of epiphyses. Radiograph of skull (Fig. 3) shows enlargement of sella turcica. Radiograph of thorax shows no substernal thyroid and no remains of thymus.



Fig. 1.—Patient in case of infantilism with absence of thyroid and tumor of pituitary.

*Course of Disease*—

	Pulse	Weight Lbs	Tempera- ture	Thyroid Grs
May 20, 1909	114			2 twice daily
May 21, 1909	114	69 3/4		2 t 1 d
May 22, 1909	114		98 4/5°	2 four times daily
May 24, 1909	132		98 4/5°	4 t 1 d
May 25, 1909	132			4 t 1 d
May 26, 1909	140	69	99 1/2°	4 t 1 d
May 31, 1909	138	69 3/4	98 4/5°	14 daily

June 12, 1909. The patient has been recumbent most of the time since last note. Pulse has been about 120 lying and about 150 sitting. Thyroid has been

gradually increased to 6 grains daily, which the patient has been taking for five or six days No change

June 16, 1909 Thyroid reduced to 6 grains daily

June 18, 1909 The patient has been feeling weak, has had slight headache for two or three days This started after perimeter examination on June 14 Patient allowed to go home Thyroid stopped Pituitary extract recommended

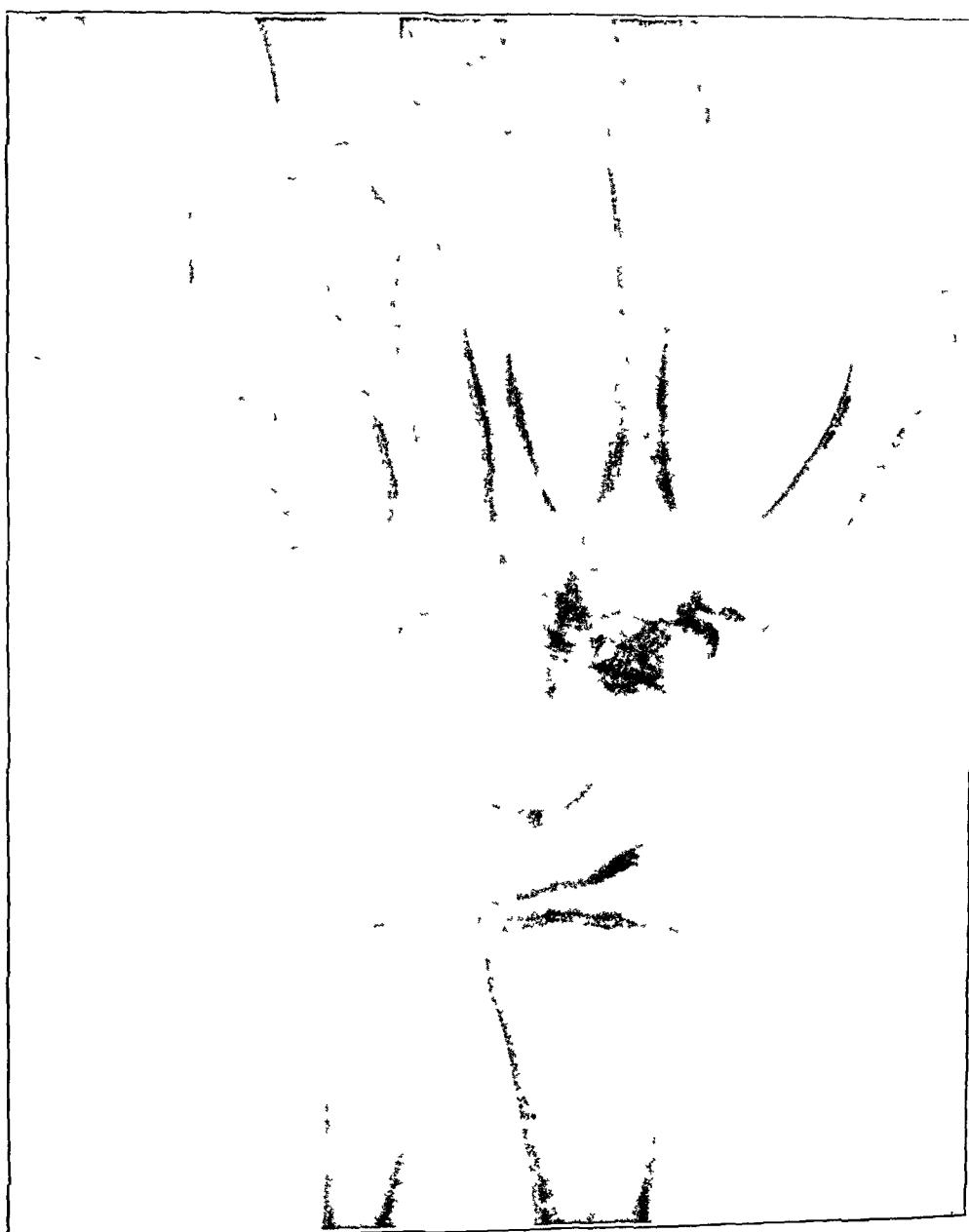


Fig 2.—Radiograph of long bones, showing lack of ossification of epiphyses

July 3, 1909 Dr. Stingley writes "Patient seemed better than when she returned Under the pituitary extract her pulse has been reduced to 96 sitting and 98 standing, with an appreciable increase in volume and pressure She now

weighs 70 pounds One thing that is of seeming importance to me is that she voluntarily states that her eyesight is improving within the last few days"

Aug 11, 1909 Dr Stingly reports "Patient continues to improve in the way of general health She says of herself, 'I never felt better in all my life' Her weight increases something more than a pound a week She is yet taking the pituitary extract, 15 minims after each meal"

Aug 19, 1909 Dr Stingly writes "Her improvement has suddenly stopped, and during the last few days she has lost two pounds of her recently acquired ten pounds She is temporarily out of pituitary extract The pulse remains within

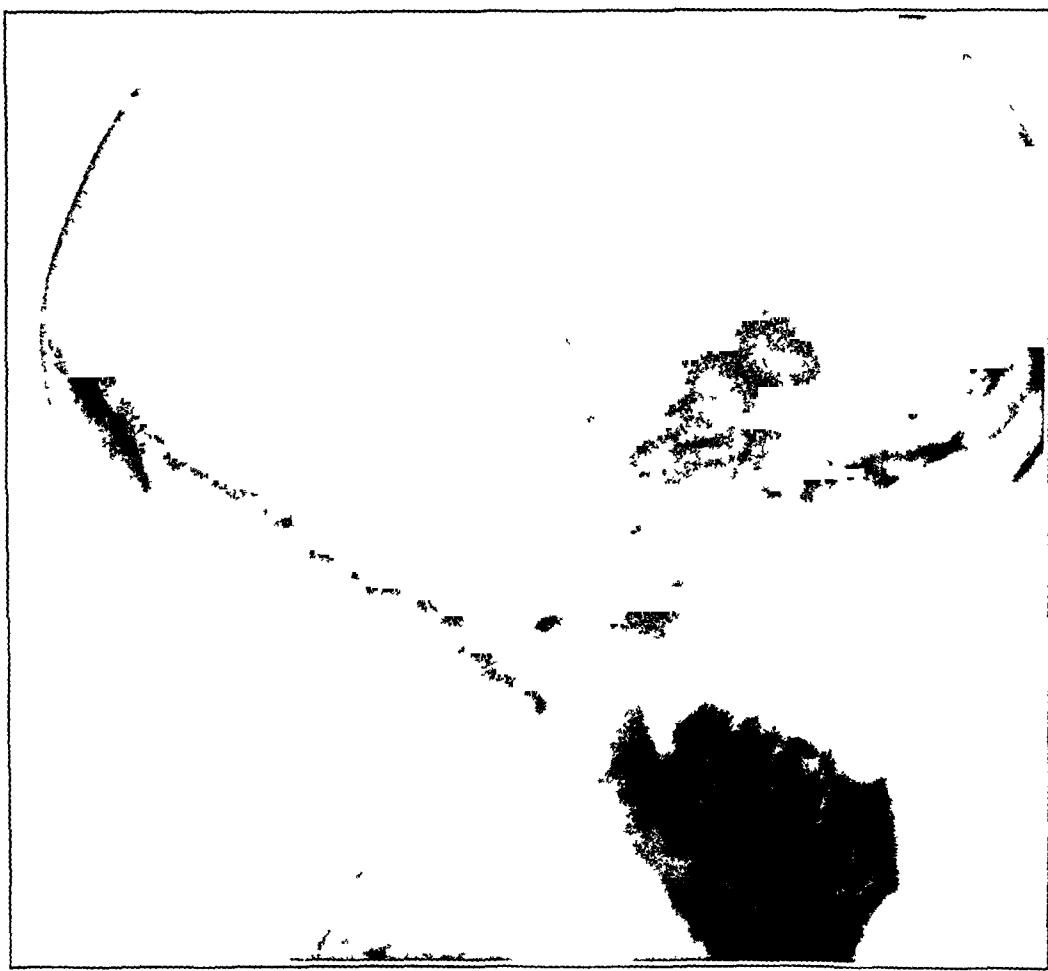


Fig 3.—Radiograph of skull, showing enlargement of sella turcica

normal range Her hair is growing, she thinks, at a rate it has not grown hitherto I think she is much better than when you last saw her "

Nov 9, 1909 Patient presented herself again She looked well The hair on the head had grown considerably She said that she had gained 15 pounds She had no headache Blood pressure, 110, pulse 100 sitting, skin, especially that of the back of the hands was dry The hemianopsia on rough test, seemed unchanged

Operative procedure has of course been considered, but the patient and her people are violently opposed to it In view of the remarkable improvement, we feel that the trial of the pituitary extract has been justified and we are still unwilling to insist on an operation at this time

*Summary of Case*—A woman of 24 years, infantile in type, and very poorly nourished, presenting no evidence of acromegaly or gigantism. Radiographs of the long bones show failure of ossification of epiphyses. Absence of sexual development. Arterial hypotension. Bitemporal hemianopsia. Intracranial pressure indicated only by frequent headaches. Athyreosis. Radiograph of skull shows enlargement of sella turcica.

#### COMMENTS

Several aspects of the case open up interesting fields of speculation. Before discussing these, a brief review of the histogenesis of the pituitary may not be out of order.

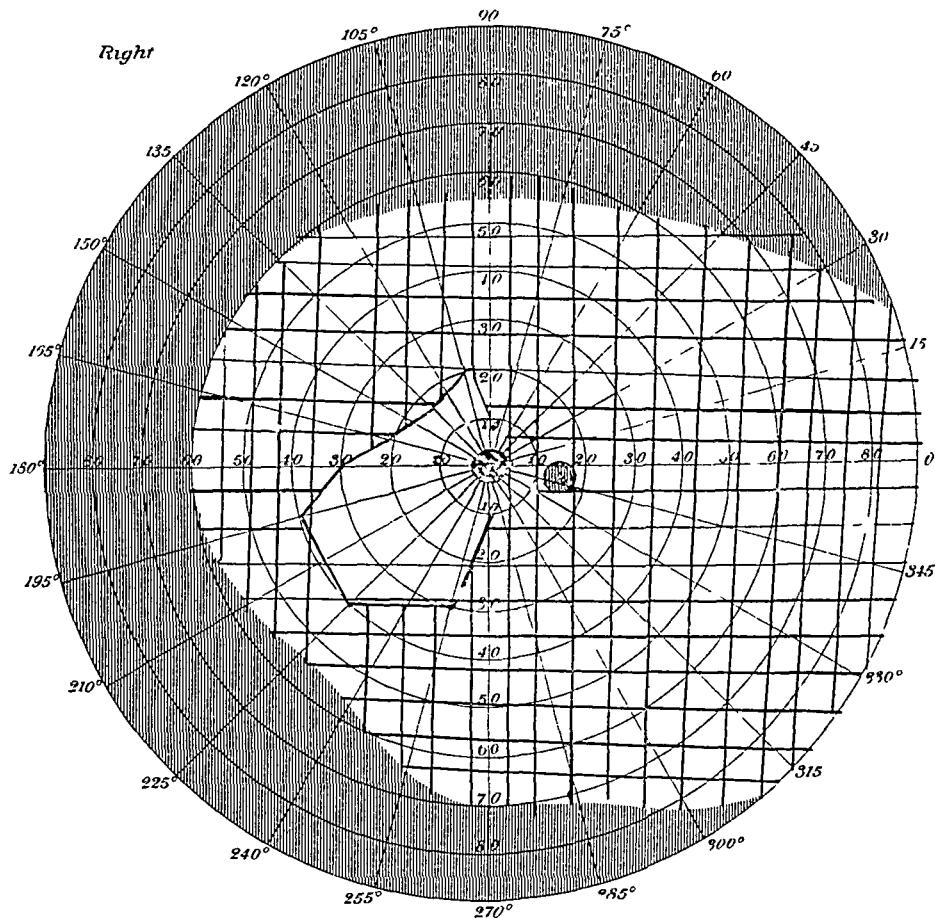


Fig. 4.—Right visual field showing hemianopsia for red

The hypophysis is developed from two distinct sources—the anterior part from a diverticulum from the buccal cavity, the so-called pouch of Rathke, the posterior part is developed from a downward growth of the second cerebral vesicle—the infundibulum. This in later life becomes intimately connected with the anterior part, but in the adult human subject it may be easily separated. The infundibular part may be divided into two portions, the nervous part proper and the intermediate part.

The latter is formed by epithelial investment of the posterior lobe with its upward extension of the outer walls of the stalk of the infundibulum. The nervous portion of the anterior lobe is made up of ependymal and neuroglial tissue, and does not contain any true nerve cells. The pars intermedia contains cells with eosinophilic granules. These cells are arranged in the form of tubes or acini, and have a tendency to secrete colloid. The anterior lobe is made up of groups of cells distributed in the neighborhood of thin-walled venous sinuses.

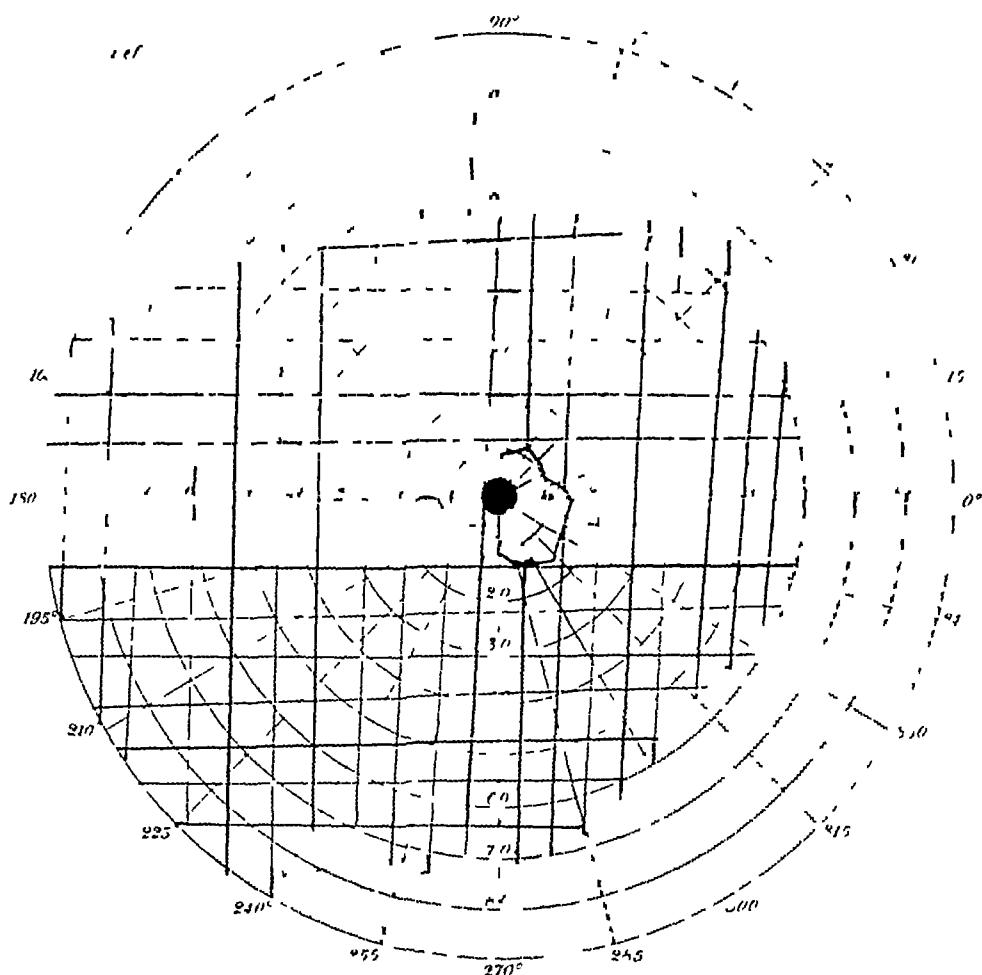


Fig. 5.—Left visual field showing hemianopsia for red.

In view of the common origin of the thyroid and pituitary, their similar structure and apparent relation in disease, it is natural that they should be supposed to be mutually supplementary and to act vicariously one for the other. Just as thyroid diseases may cause adiposity and myxedematous conditions of the skin just so these changes have been noted in connection with hypophyseal changes. Von Reuss noted hemianopsia in the course of the fourteenth, fifteenth and sixteenth

pregnancies, and its disturbance during the puerperium. He attributed this to hypertrophy of the hypophysis at this time. This is analogous to the enlargement of the thyroid during pregnancy. Rogowitsch, Gley, Stieda and others have observed hypertrophy of the pituitary when the thyroid was removed. Rogowitsch also believed that the non-occurrence of symptoms after thyroidectomy in rabbits is explained by the comparatively large size of the pituitary in these animals. Coulon, however, found in five cretins, both thyroids and pituitaries atrophied. Boyce and Beadless have found the pituitary enlarged in myxedema cases. There are,

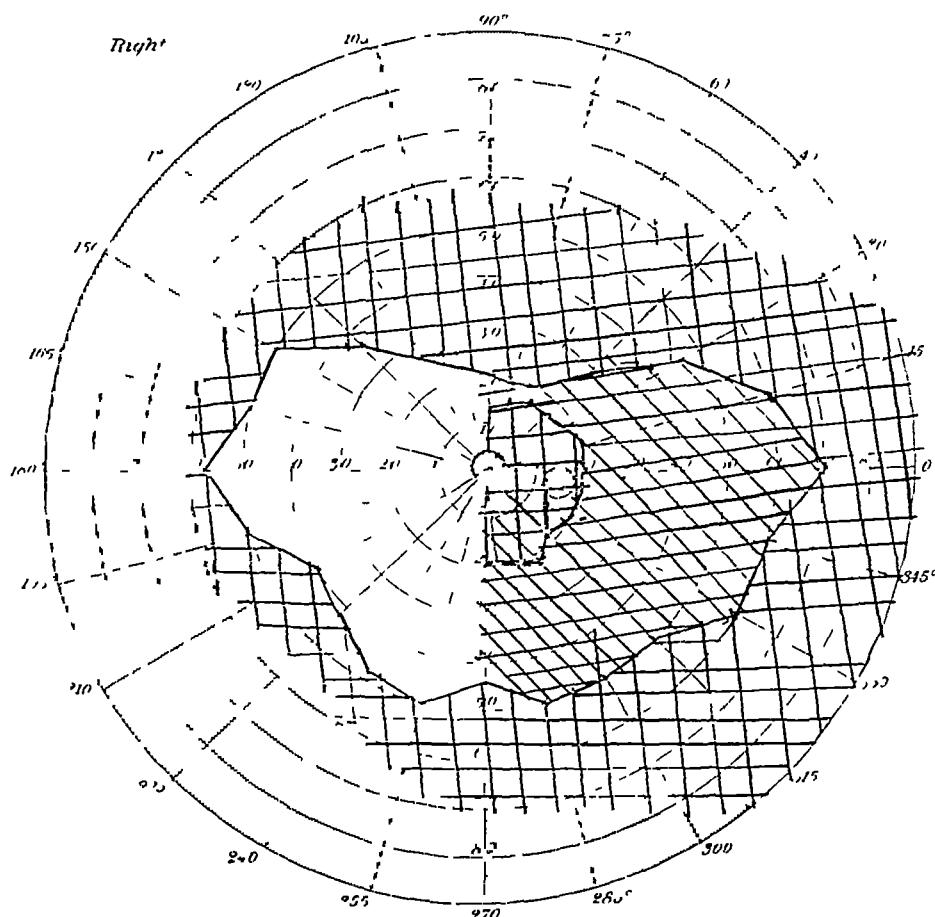


Fig. 6.—Right visual field showing complete and partial loss of white vision in temporal half.

however, observations which go to show that changes in one gland may exist without changes in the other. It seems to us, therefore, natural to suppose that the absence of the thyroid in our patient stands in direct relation to the enlargement of the pituitary. May it not very well be that the pituitary, in acting vicariously for the thyroid (which for some unknown reason has failed), has become enlarged? The idea is not a

new one, but there are widely divergent views as to which portion of the pituitary is affected consequent on removal of the thyroid. *A priori*, one would suppose that on account of its similar structure and origin, it would be the anterior lobe of the pituitary which would be affected. Rogowitzsch, Stieda Gley, Holmeister, Pisenti and Viola, Schonemann and others, indeed have reported changes in the anterior lobe consequent on the removal or disease of the thyroid. Hering, on the other hand, controverts this, and concludes from a series of experimental thyroid-

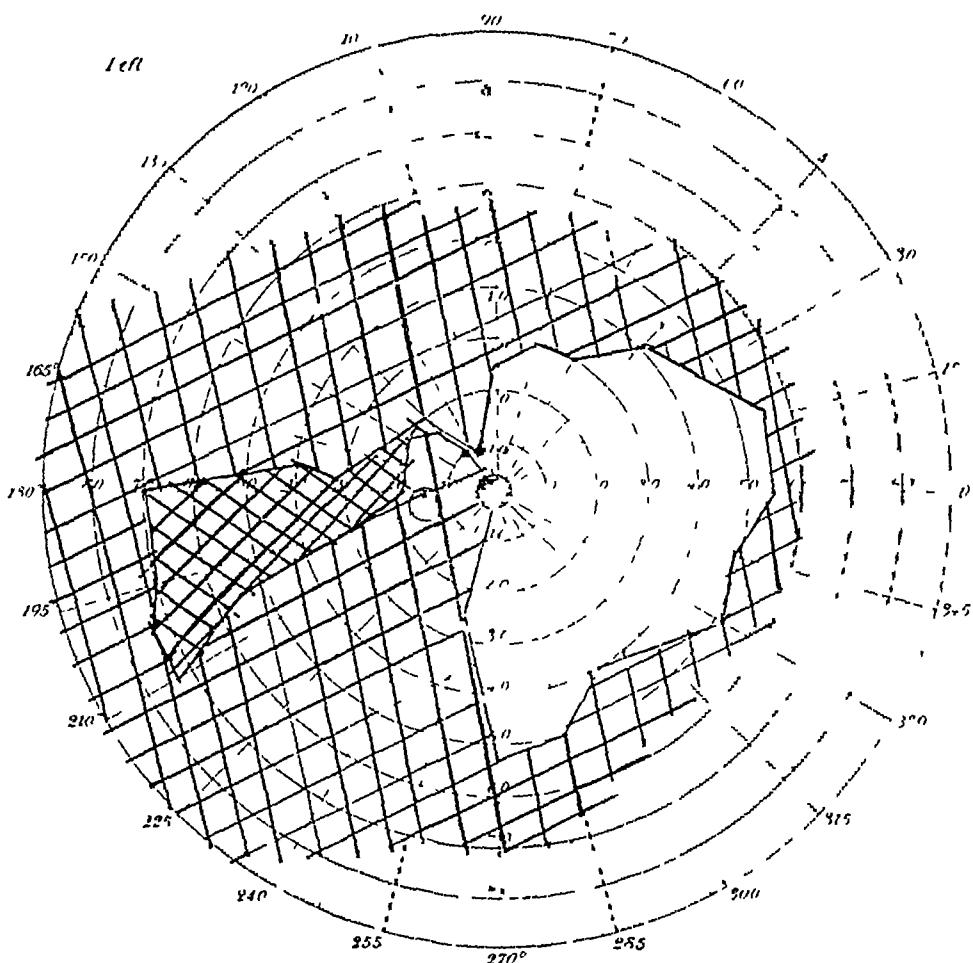


Fig. 7.—Left visual field showing complete and partial loss of white vision in temporal half.

ectomies on rabbits, cats and a dog that the operation causes no change in the anterior lobe at all but in the posterior lobe.

Removal of the thyroid body results in an increased production of colloid by the pituitary. The normal mode of secretion by the posterior lobe of the pituitary, which is the only lobe concerned in the production of colloid appears to consist in a conveyance of granular or hyaline material by cells of its epithelial covering, invading and passing through the pars nervosa into the infundibular recess, when the cells break down to liberate their products into the cerebrospinal fluid.

Thyroidectomy brings about an exaggeration of the process. How far the changes are to be regarded as compensatory for the loss of the thyroid is not yet determined. Their relation to the production or amelioration of the symptoms which in many animals follow removal or disease of the thyroid is also a matter for further investigation.

The fact that thyroid feeding did not benefit our patient (though she reacted promptly and easily) might be interpreted in one of two ways. In the first place, we might assume that the vicarious action of the pituitary had been quite sufficient and that any additional thyroid action was not only superfluous, but harmful. Or, we must assume that the absence of the thyroid has been a coincidence and has played no part in the clinical picture she presents. We are inclined to the former view.

We would like to suggest further that the vicarious enlargement of the anterior lobe has by pressure caused interference with the function of the posterior lobe. It is well known that while the extract of the anterior lobe is physiologically inert, that of the posterior lobe has a powerful blood-pressure-raising action similar to that of adrenalin. Since the patient has been taking the extract of the posterior lobe she has improved. In this connection we wish to suggest a modification of the classification mentioned by Harvey Cushing in the summary of his admirable oration at the last meeting of the American Medical Association. He catalogues the disturbances of the pituitary under the headings of hypofunction and hyperfunction of the anterior lobe. We think it is necessary to consider hypofunction and hyperfunction of each lobe separately, as it seems more than likely that their functions are distinct and separate.

The relation of the hypophysis to the other glands with internal secretions, the adrenals, the sexual organs and the thymus also calls for attention. Has the failure of sexual development in this patient been dependent on a lack of an unknown substance which the hypophysis should supply in order to stimulate the sexual organs to put forth in their proper turn their internal secretion? Or is the failure of sexual characteristics independent of the pituitary disease and due solely to primary conditions in the sexual organs themselves? It would be interesting to determine whether ovarian extract would cause this woman to develop breasts and pubic and axillary hair. What might testicular extract do for her?

And finally, the skeletal changes are to be explained. There is a long-known connection between acromegaly and pituitary tumors. If hypophyseal disease may cause hypertrophy of the bones of the extremities, is it not plausible to suppose that it is also responsible for the failure

of the epiphyses to ossify properly? We consider, therefore that the bone condition in our patient is directly due to the hypophyseal changes

In conclusions we offer the following suggestions

1 There has been an enlargement of the anterior lobe of the pituitary acting vicariously for the thyroid

2 This large anterior lobe has caused an interference with the posterior lobe causing (a) low blood-pressure (b) failure of stimulus to sexual organs, (c) failure of ossification of epiphyses

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## A CASE OF TRICHINOSIS, WITH RECOVERY OF PARASITE FROM THE BLOOD AND MUSCLE

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DIS Herrick and Janeway<sup>1</sup> report the first case of trichinosis in which the embryo of the parasite was found in the blood. We wish to record here another, which, so far as we know, will be the second case. The history is as follows:

*Patient*—C. S., Case No. 857, male medical ward, South Side Hospital, admitted Dec. 24, 1909, with the diagnosis of acute nephritis, which was made by the resident on the ambulance service, being based mostly on the facial edema, which involved the eyelids very markedly. After the patient was in the ward for several days, it was found that, so far as could be estimated by the urinalysis, the kidney condition alone did not seem to be severe enough to account for the marked facial edema, especially as it persisted after the albumin and casts had disappeared from the urine by the third day. The patient, being an Italian, could not give a very definite and satisfactory history of the onset of the disease, so that he was treated symptomatically for about a week. The most prominent subjective symptom was muscular pain. For this he was given salicylates, which had, so far as could be seen, no beneficial effect. There were no symptoms that were suggestive of muscular rheumatism other than the muscle pains, and even these were too definitely localized within the belly of the muscles. On entrance, the patient's pulse was 105 and temperature 100 F., the fever and acceleration of the pulse subsided within four days and remained at about the normal point until he was discharged.

*Examination*—On Dec. 29, 1909, a leucocyte count of 11,000 was reported, but this was passed over as insignificant. On Jan. 6, 1910, it occurred to one of us that the patient might be suffering with trichinosis, and a leucocyte and differential count was at once made. The blood examinations were made by the junior author of this paper. January 6 Leucocytes, 13,400 per cubic millimeter, polynuclears, 62.5 per cent, small mononuclears, 18 per cent, large mononuclears, 1 per cent, transitioningals, 0.5 per cent, eosinophils, 17 per cent, mast cells, 1 per cent. The eosinophilia with the two clinical symptoms, facial edema and muscular pains, supported the correctness of the suspected diagnosis. Blood examinations every other day for over a week showed that this eosinophilia varied from 17 to 25 per cent, while a mild leucocytosis persisted. On Jan. 7, 1910, following the method of Staubli, 10 cc. of blood were taken from the median cephalic vein, diluted and centrifuged. After a search of several hours, two embryos of the parasites were found in one field. These corresponded exactly in size, form and character to the photograph in Herrick and Janeway's article, and

\* The case was reported at a regular meeting of the Pittsburgh Academy of Medicine, Jan. 25, 1910.

<sup>1</sup> Herrick, W. W., and Janeway, T. C. Demonstration of the *Trichinella spiralis* in the Circulating Blood of Man, THE ARCHIVES INT MED., 1909, III, 263

were studied by both of us leaving no doubt as to the nature of our findings. As it happened on a Sunday evening it was impossible for us to have a photomicrograph taken. Two days later another search of the blood was made but this proved negative. On Jan. 23 1910 a small piece of the left gastrocnemius was removed and in this a large number of parasites were found one of these was photographed. The great numbers of parasites found within a very small piece of muscle seemed remarkable.

Later history of the case developed the facts that in the boarding house in which this patient lived, four others were afflicted with the same ailment and that they all ate pork frequently. Furthermore it was determined that at the onset of this attack the patient had had gastrointestinal symptoms of moderate severity.



Trichinæ found in a small piece of the left gastrocnemius

#### SUMMARY

All considered the subjective symptoms in the case as it presents itself to us were as follows. Gastro-intestinal disturbance, followed by general illness of which edema of the face and severe pain in the muscles were the main features.

The objective symptoms were edema of face moderate fever temporary albuminuria and cylindruria painful tender and swollen muscles, mild leucocytosis and a marked eosinophilia. This led to the clinical diagnosis which was verified by finding embryos of the parasite in the blood and further developed parasites in the muscles.

Fifth Avenue and St. James Street—4502 Fifth Avenue

## BOOK REVIEWS

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HISTORY OF YELLOW FEVER By George Augustin, Assistant Secretary, Louisiana State Medical Society Cloth Pp 1194, with illustrations Price, \$6 00 New Orleans Published for the author by Service & Pfast, 724 Perdido Street 1909

Yellow fever has been annihilated in its classic abodes—Cuba and the Isthmus of Panama. A turning-point in its history has been reached, and though the history of the discovery of the cause has still to be written, it is not likely that the epidemiologic chapters will ever be repeated, and it therefore seems fit material for the historian. The present work is evidently a labor of love, and the author deserves much praise for doing as well as he has. He would doubtless receive more had he not offered so much. Nearly forty pages are given to a description of other epidemic diseases, with many curious bits of medical history thrown in. This is preceded by a chapter on definitions and considering that the book is intended partly for "the information and guidance of the public," it is unfortunate this could not have been done by a trained hand. The definitions of "infection" and "contagion" for example, are such as might have been written in the fifteenth century and squarely state that yellow fever is not infectious (p 3). A chapter on "Insects as Propagators of Disease" is interesting but does not mention the most remarkable forerunner of Finlay's discovery, whose name appears in a bibliographic list near the end of the book. The "Preliminary Observations" end with a chapter on the "Cradle of Yellow Fever," which the author thinks was Asia. Following this is a "History of Yellow Fever by Localities," omitting with an apology, the West Indies and South America, and filling, even with that omission, nearly 900 pages. The toil necessary for such a compilation must have been colossal, but the value of the material can be known only to those who are obliged to try to get something out of it. There is no index to this or any of the other numerous data. The remaining 160 pages are devoted to the epidemic of 1905. The history of that epidemic well deserves to be made accessible to the medical, as well as the lay reader. In the present form, the chapters have an additional interest because they were written by actual participants in the struggle. The chapters on diagnosis, by H. P. Jones, pathology, by O. L. Pothier and prognosis, by Chassaignac, are most interesting. The chapter on treatment is written by one who claims to have treated "over 230 cases without a death" a statement that might well discourage others, especially when they learn that the author thinks it proved that yellow fever is not caused by a microbe. When we learn that he was once secretary of a state board of health we can understand some of the difficulties of public health in his section of the country. The book should be in every medical library, notwithstanding the difficulties that attend its study and use.

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LEHRBUCH DER KRANKHEITEN DES HERZES UND DER BLUTGEFÄSSE By Dr Ernst Romberg, Director of the Medical Clinic, Tübingen Second edition Price cloth, 14 marks Pp 473, with 69 illustrations Stuttgart Ferdinand Enke 1909

The appearance of the second edition of Romberg's "Diseases of the Heart and Blood Vessels" will be welcomed by every one who is familiar with the previous edition or who desires a clear and concise work on this subject.

In the introductory chapters the author refers to the recent development of accurate methods for studying the heart by instruments such as the sphygmograph, cardiosphygmograph, electrocardiograph and orthodiograph and the danger of overestimating the value of these newer methods and drawing conclusions from observations obtained by a single method of observation. He considers these newer methods as valuable aids rather than means that will dispense with our previous methods of examination. The interesting subject of means of determining the functioning power of the heart is reviewed and the conservative conclusion drawn that all of our present methods for determining the functioning power of the heart are inaccurate and some of them dangerous. He refers especially to the fallacy of laying too much stress on the value of blood-pressure and pulse rate. The chapters on valvular lesions and chronic insufficiency of the heart muscle are especially complete and well arranged and the subject is considered in a very logical and sane manner. In the discussion of acute endocarditis the value of blood cultures in the diagnosis is not sufficiently emphasized. The treatment instead of being discussed at the end of each chapter is postponed and taken up after the discussion of valvular and muscular cardiac disturbances. This permits of greater clearness and avoids needless repetition. The author devotes 98 pages to the discussion of the treatment of these two conditions. Nothing even in the slightest detail of treatment has been omitted and, on the other hand methods of treatment or drugs recognized as of little value are merely referred to. The physiological action, indications and contraindications for digitalis are presented very completely. The author calls attention to a fallacy too widely disseminated that digitalis is contraindicated in aortic insufficiency and diseases of the heart-muscle. Like most German physicians, he prefers the powdered leaves or an infusion of digitalis. As the plant grows abundantly in Germany, and stringent laws compel the pharmacist to renew the leaves each year this advice is good but not necessarily applicable to America where we import our leaves and where the supply on hand must be disposed of before new leaves are purchased. The titrated tincture is well spoken of. The value of the book is enhanced by an excellent bibliography pains having been taken to insert the exact title of the paper referred to rather than merely the author's name and the title of the journal in which it was published. An omission too common in all German publications is adequate reference to American literature. The illustrations although not numerous are well executed and enhance the value of the book. The author's wide clinical experience and his conciseness and clearness of expression render the book of great value to those interested in cardiovascular diseases.

**TUBERCULOSIS** A Treatise by American Authors on Its Etiology, Pathology, Frequency, Semiology, Diagnosis, Prognosis, Prevention and Treatment. Edited by Arnold C. Klebs M.D. Cloth. Pp. 939 with 3 colored plates and 243 text illustrations. Price \$6. New York D. Appleton & Co. 1909.

In preparing a review of this volume the reviewer fully appreciates that it is always much easier to criticize than to construct. It should be within the province of a reviewer to emphasize meritorious aspects of a work as well as to note possible defects. It is impossible however within the limits of this article to consider the points of excellence as fully as desired. The list of contributors would lead one to expect a volume of exceptional worth and indeed several articles are especially good. Several others which deserve some criticism nevertheless contain much useful information and the writers are entitled to favorable mention. While some portions are particularly praiseworthy the production *in toto* must be regarded as something of a disappointment. Before commenting on the individual articles it is well to note a few features peculiar to the book as a whole.

The same subject is occasionally discussed by two or more authors and differing opinions are sometimes expressed. For example, Minor and Ravenel disagree as to the use of the Gabbett stain, Ravenel describing it on page 16 as "a very convenient method for the practitioner." Minor, on page 330 states that the method is "uncertain and should never be used." Ravenel states on page 35 that "the digestive tract is an important if not the most important avenue of entry for the tubercle bacillus." Von Pirquet on page 143, states that "this route seems to play a very insignificant rôle." In administering tuberculin, Minor recommends "driving the needle vertically into the muscles up to its socket, which avoids all veins and is less painful than the subcutaneous method" (page 342). Brown, on page 523, insists that the tuberculin "should be given subcutaneously."

Not only is such conflict of ideas exhibited by different writers, but inconsistencies by the same author occasionally appear. Thus Brown, on page 532, states that an increase of cough and expectoration following the administration of tuberculin "is not the writer's experience. In many instances both cough and expectoration are reduced following the injection." On page 553 he says, "The cough and sputum are frequently increased after tuberculin."

A curious feature of the book is the mass of "Addenda" which is taken from the published abstracts of papers presented at the International Congress on Tuberculosis. Some of this is quite irrelevant to the subject matter of the respective chapters. The book would have been materially improved had the editor taken pains to institute a selective review of these abstracts and incorporated those worthy of inclusion in the text in their appropriate places.

Among the important omissions may be noted the absence of any description of tuberculosis of the pleura, tuberculosis of the mediastinal and mesenteric glands, tuberculosis of the appendix or of the gums, tongue, and palate. It is singularly unfortunate that there should be no discussion of the etiology, pathology, course, symptoms or diagnosis of pleurisy, either existing alone or as a complication of pulmonary tuberculosis. The whole subject of empyema is disposed of in six lines and pneumothorax in a very few lines, while no mention is made of pneumopyothorax. A book of this scope should contain a thorough and comprehensive consideration of general military tuberculosis. While the pathology is ably discussed by Dr. Hektoen the clinical features of the typhoid and pulmonary types are described very briefly in another portion of the book. Meningeal tuberculosis is not discussed, save from a purely surgical standpoint by Dr. McArdle. The reviewer is unable to find any reference to the research work at the Phipps Institute.

Notwithstanding these regrettable omissions the book bears evidence of most consistent "padding" throughout. This is repeatedly shown by the blank portions of the pages at the end of each chapter, by the unnecessary spaces allotted to tables, charts and diagrams, and by the character of the illustrations. As a single example of the padding to which the publishers have resorted the reader is referred to page 749, nearly all of which is unfilled, and to the following page 750, on which two short paragraphs are permitted to constitute an entire chapter. Another instance which is similar to several throughout the book may be found on page 387, four-fifths of which are blank and all of the three following pages

A few of the illustrations are worthy of commendation, notably the radiographs of different stages of pulmonary tuberculosis, the figures in the chapter on "Tuberculosis of the Bones and Joints," and Plates II and III. There are but three colored plates, two of which are original. The illustrations of pathologic specimens are not especially good. Ten complete pages are devoted to the showing of thirty-eight charts of various stages of tuberculosis. Many of the illustrations, particularly in the chapters on prophylaxis appear of but slight, if any, practical value. Some of these have already appeared several times in former articles. It is difficult to conceive how any special lesson can be imparted by the

picturing of ordinary baskets, shovels spades forks and pickaxes, made use of by pulmonary invalids. In Appendix VII, entitled "Devices for the Prevention of Tuberculosis" we find from pages 832 to 853 60 illustrations representing various kinds of cuspidors, pocket flasks, suction masks, reclining chairs, portable cots, tent frames etc., reminding one of the advertising catalogue of a surgical instrument house.

In reviewing the various chapters attention can necessarily be directed to but a few features. The introductory articles by Drs Osler Trudeau and Biggs cannot fail to be of interest to the reader who however must experience a degree of disappointment in their extreme brevity. Dr Osler's contribution consisting of eight pages of historical matter, Dr Trudeau's two and one half pages and Dr Biggs' about one and one half pages.

Chapter I, on "The Tubercle Bacillus" by Dr Mazev P Ravenel is especially good and constitutes one of the excellent features of the book. It is to be regretted, however, that a most important subject, "The Transmissibility of Bovine Tuberculosis to Human Beings," is disposed of in a page and one half among the "Addenda." Dr Ravenel's discussion is largely confined to a brief reference to the "conference in camera" at the International Congress on Tuberculosis at Washington. He does not present a comprehensive report as to the present status of this vitally interesting question. The reviewer suggests that confusion may arise from using the term "pseudotubercle bacilli" as synonymous with acid fast bacilli. Under "The Mode of Invasion" no reference is made to Svensson's recent experiments. The names "Twichell" and "Hidyo" are misspelled.

Chapter II, on "Tubercle and Morbid Anatomy," by Dr Ludwig Hektoen is admirably presented and is indeed one of the strongest articles.

Chapter III, entitled "Resistance Predisposition and Immunity" by Dr Edward R Baldwin, is an able concise review of the subjects as might be expected from this writer. The name "MacFadyan" is misspelled.

The chapter on "The Frequency of Tuberculosis" is written by the editor Dr Klebs. Several pages are devoted to the insertion of tables and diagrams taken from the twelfth United States Census Reports. The treatment of the subject is somewhat elementary. Little attention is paid to grammatical construction, an instance being noted in the incorrect English in his very first sentence.

The chapter on "Tuberculosis Among the Dark Skinned Races of America," by Dr Thomas D Coleman, is of considerable interest but exhibits evidence of hasty preparation. A large proportion of the text concerning tuberculosis in the Indian is composed of quotations from other writers.

The chapter on "Frequency of Tuberculosis in Insane Asylums" by Dr Rich and C Hutchins is interesting, well written and suitably illustrated.

The chapter, "Tuberculosis in Childhood" by Dr Clemons von Pirquet comprises seven pages of material for which the editor adopts a semiapologetic tone in the footnote by stating "This article does not undertake to review the subject systematically. Nevertheless the contribution although of a brief introductory nature and inserted in the general symptomatology is of much value. It is unfortunate, however that in a book of this size so important a subject as tuberculosis in childhood is not accorded more complete and systematic treatment."

The chapters on "Symptomatology of Pulmonary Tuberculosis," "Physical Examination and Diagnosis" by Dr Charles L Minor are worthy of detailed mention. Much that he has written is excellent although the arrangement is not always as logical or the manner of presentation as clear concise and forceful as might have been expected. The author has in many instances made references to the literature instead of giving the results of his own personal observation. For the general practitioner this detracts from the value of the contribution. Dr Minor devotes much time and space to the physical signs of early tuberculosis,

without due and proper emphasis on those features which are of the most common occurrence and of chief importance. The article on the Roentgen ray is especially interesting, as are also those on the blood and metabolism. Much valuable information may be obtained through perusal of the article on "Objective Signs" and the chapter on "Physical Examination." The attention to detail exhibited in the examination of the patient cannot be too highly commended. A review of Di Minor's articles however, which comprise a large portion of the book, must include mention of some inaccuracies of statement and a few omissions. These defects are not always of a very serious nature, and it is of course impossible in a contribution of this length to expect that mistakes can be entirely avoided.

It is not always true that the tuberculosis which develops after pregnancy is necessarily of an acute, rapidly advancing bronchopneumonic type as implied. On page 156 the author lays too much stress on the undue dyspnea and cyanosis "as the two most typical symptoms" of the typhoid type of miliary tuberculosis. These manifestations may be quite insignificant in the typhoid variety, but represent the two most characteristic features of the pulmonary type of miliary tuberculosis. On page 157, Di Minor describes the "bronchopulmonary form" as beginning with a "not very diffuse bronchitis showing isolated areas of catarrh of the fine tubes." In general the initial physical signs relate to a very widely diffused bronchiolitis, the chief distinguishing feature being the distribution of very fine rales throughout the entire bronchial tract. On page 169 Di Minor advocates the use of the coal-tar antipyretics for fever, which is not in strict accordance with modern ideas. On page 197 he says, "Dysphagia is practically never present in early cases of tuberculous laryngitis." Such a statement is, obviously, incorrect, as this symptom depends entirely on the location and character of the tuberculous process in the larynx. In cases of early ulceration of the epiglottis and arytenoids the dysphagia may be the very first subjective manifestation of laryngeal infection. On page 202 he says, "Laryngeal cough is easily recognized by its paroxysmal nature, dryness, great intensity and peculiar timbre." This statement needs considerable modification as the differentiation of laryngeal coughs from those dependent on other conditions is hardly as simple as described. On page 216 he speaks of the premonitory streaking of the sputum with traces of blood which often precedes the bleeding for some days, and advocates blistering over the site of congestion in order to avert later hemorrhage. Waiving any criticism of the rationale of such a procedure, attention is called to the frequent impossibility of recognizing the "site of congestion" over which blisters may be applied. Examination of the chest at such a time should be avoided. On page 217, septic aspiration pneumonia following hemorrhage is disposed of in three lines in which appear the statement that "the fever continues without remission until it clears up." It is well known that this form of pneumonia rarely "clears up," but is in most cases fatal. The statement, therefore, that "if dissemination follows the pneumonia the temperature persists" is subject to some criticism. The author appears to exaggerate the value of mensuration, which many clinicians believe to be of but slight practical utility. No mention is made of the very considerable variation in the chest expansion according to the type of respiration in individual instances, the position of the diaphragm as ascertained by abdominal measurements evidently being regarded as a negligible factor. On page 266 it is stated that metallic tinkling "is only found in pneumothorax and large cavities." Metallic tinkling is seldom, if ever, recognized in pure pneumothorax, but chiefly when there is liquid as well as air in the pleural cavity or in large pulmonary cavities. On page 267 the author states that the amphoric voice "is most typically heard in pneumothorax, and, like amphoric breathing, if pneumothorax can be excluded it is a positive sign." He undoubtedly means that the amphoric voice is a positive sign of cavity formation provided pneumothorax can be excluded. His statement, however, that it is most typically heard in pneumothorax needs qualification as

it is capable of recognition especially in the open type rather than in the valvular or closed variety. On page 285 the author is again careless in his use of the term "pneumothorax," describing a typical fluoroscopic picture of pneumothorax but referring to the condition as pneumothorax. The author neglects to differentiate the various types of this condition, and on a later page speaks of the sudden dyspnea, the cardiac dislocation, the bulging chest, the amphoric breathing, the tympanitic resonance and the large resonant rales. It should be remembered that the amphoric breathing and large resonant rales are recognized only in the open variety and that in such cases the bulging chest, which is present in the valvular type, is not found. It is impossible to conceive of all these symptoms and signs as being present in a single case. When the dyspnea is well marked and becomes progressively worse the bulging may be very apparent and the cardiac dislocation pronounced, but in such cases there is no continuous open communication with a bronchial tube, and hence no amphoric breathing or large resonant rales but, on the other hand, marked diminution of the intensity of the respiratory sounds. On page 330 the author states that the smegma bacilli "decolorize easily in alcohol." The decolorization of the smegma bacillus in alcohol is not always so easy as might be inferred some observers insisting that the absolute differentiation from the tubercle bacillus is sometimes possible only by means of inoculation tests. On page 355 it is stated that "tuberculosis, when cavities are present, is also always bilateral."

There are also noted some omissions. On page 152, in the description of fibroid phthisis, no mention is made of emaciation, which is an almost invariable feature. Dr. Minor omits all mention of the meningeal form of miliary tuberculosis. In discussing the so called inverse type of fever it is not stated that this is occasionally an accompaniment of miliary involvement. On page 184 the author briefly considers tuberculosis of the pharynx but without description of the characteristic appearances of tuberculosis of the soft palate or tongue. He states that the tonsils "show no special ocular changes." Under the subject of gastric or intestinal symptoms the psychoneuroses in dyspeptic consumptives are not discussed. Dr. Minor properly speaks of mapping out the stomach in many invalids, but the reader is not informed that this is often difficult and the results uncertain. No allusion is made to the use of bismuth and the utilization of the x-ray for this purpose. The author overlooks the fact that the frequent annoyance occasioned by the presence of tenacious mucus in the air tubes is sometimes alleviated by the judicious administration of the iodids. On page 330, Dr. Minor discusses "diagnosis by means of animal inoculations." He neglects, however, to mention the recent work of Bloch in extirpating the regional lymph-glands at the end of two weeks then crushing and subsequent examination for tubercle bacilli. He also fails to allude to the experiments of Larrier Ronzoni and Hirschboim, who effected a considerable saving of time by injecting suspected material into the mammary glands of guinea pigs and rabbits which were suckling their young.

The style may at times be subject to criticism, as for instance the following expressions: "The feverishly bright eyes looking at us for help from the bottom of deep pits" (page 151), page, 172, "The whole body seems filled with 'tiredness.' If the patient lies down to rest weariness seems to run through his limbs. They ache with fatigue and seem to pin him to the bed." The writer's sentences are sometimes of such length as to suggest a lack of terminal facilities as for example on page 325 there is a sentence of over ten lines, one of seven and another of eight lines.

The grammatical construction is occasionally incorrect as for instance page 162, "more absolutely accurate," page 313, "most perpendicular" "Adventitious" is misspelled.

Let it not be understood that Dr. Minor's contribution as a whole possesses other than a high order of merit. Notwithstanding the defects to which attention has

been called, many portions of his articles are exceedingly good and deserving of very favorable comment. In view of the importance of these chapters and the fact that they represent so much of the text the reviewer has felt constrained to devote disproportionate space to their consideration.

Baldwin's article on "Individual Prophylaxis," although brief, is interesting and in general well written.

The chapter on "Public Measures in the Prophylaxis of Tuberculosis" is written by Dr S A Knopf, and contains much of interest to the laity as well as to the profession. His contribution, however, in the way of subject-matter and illustrations represents much that is taken from his previous papers. In addition, out of 90 pages, approximately one third consists of quotations from articles by other writers. The inspection of food-supply is briefly treated, while the sanitation of workshops, factories, etc., is dismissed in a few lines, most of which are devoted to the advocacy of securing proper receptacles for the expectoration.

The chapter on "Specific Treatment," by Dr Lawrason Brown, is of especial interest and value, but the reviewer is unable to agree with a few statements of the author. He states on page 543 that "a tendency to hemoptysis is no contraindication" for the administration of tuberculin. Dr Brown's experience is at variance with that of some clinicians in this respect. Even slight but frequently recurring hemorrhages should at least compel the utmost caution in the administration of tuberculin if not its discontinuance. He says, "If tuberculin be of value for patients failing to improve under other forms of treatment it is of much more value for patients in incipient stages." In the opinion of the reviewer it cannot be assumed that because this agent is occasionally of benefit to selected patients having failed to respond to other measures of treatment, it must necessarily be of value to all patients in the incipient stages regardless of important considerations. Dr Brown states on page 545 that "members of phthisical families even though they present no signs or symptoms of disease are often benefited by tuberculin (Sahli)." It does not appear that our knowledge regarding tuberculin therapy is thus far sufficient to justify its widespread administration to individuals exhibiting no manifestations of disease. On page 555 the author states that "all forms of surgical tuberculosis are apparently benefited by small carefully selected doses of tuberculin when the patient is in a suitable condition to take tuberculin." This does not obtain with reference to tuberculosis of the cecum and the appendix. In such cases the diarrhea and other abdominal symptoms are likely to be aggravated very materially by the administration of tuberculin. Even tuberculosis of the cervical glands, the epididymis and testis, although occasionally benefited by this agent, are not infrequently influenced quite unfavorably. These conditions represent important forms of surgical tuberculosis and are so included in Part VI of the contents. In speaking of tuberculin on page 557 Dr Brown says, "The results in a large number of selected patients can be said to be practically always favorable." On page 565 he says, "The present status of tuberculin may be expressed in a few words. Tuberculin when properly given does no harm," etc. It is suggested that these statements should be somewhat modified. It should be made clear that the indiscriminate use of tuberculin by the general practitioner as a routine method of treatment of pulmonary tuberculosis is an extremely unwise procedure. Dr Brown makes no mention of the effect of tuberculin on the dysmenorrhea of tuberculous women. Bacterial vaccines, to which the attention of the profession has been directed during the past few years, are dismissed in three lines in which the author states that they have been employed, but gives no results of personal observations or of the experience of others. Among other "false specifics" he fails to allude to the so called "mercury treatment" which, in view of its rather unfortunate use at the present time among general practitioners, should at least be commented on in a book of this description. Instances of incorrect English are occasionally noted. The name "Mifuccci" is misspelled.

The chapter on "Specific Therapeutics" is written by Dr Gerald B Webb and is of much interest. In his published results of 50 cases of patients inoculated by the author with homologous vaccines prepared from the mixed organisms he fails to give any description of the cases. The reader is left in doubt as to whether or not these were febrile and advanced phthisical patients, exhibiting clinical manifestations of septic absorption, or whether the administration of the vaccines was based on the mere fact that the mixed organisms were found in the sputum regardless of the stage of the disease or its degree of activity. No mention is made as to the condition of the patients, the length of residence in Colorado Springs, the effect of climatic change or the previous results of hygienic and dietary methods of treatment.

The chapter on "Hygiene, Diet and Open Air in the Treatment of Tuberculosis" is by Dr Thomas D Coleman. The views expressed as to the management of the disease are for the most part rational and in accordance with modern ideas. There is exhibited, however, some carelessness in construction. On page 610 Dr Coleman says, "With reference to cuspidors, while they are frequently spoken of in derision as an American invention, the writer, as an American, is glad to acknowledge their paternity." It hardly appears that "paternity" is a proper word to use with reference to cuspidors. Of much more importance, however, are a few misstatements and omissions. On page 631 the author says, "No incipient and few advanced cases of tuberculosis die from the immediate effects of hemorrhage." No indications or contraindications are given for the performance of aspiration. He states on page 637 that "in the case of empyema the pus should be removed as soon as the diagnosis is made." The reviewer believes that this is not always rational, but that the course of treatment should depend largely on important modifying circumstances. The author says, "In the majority of cases this may be effected by making a free incision in the midaxillary line between the sixth and seventh ribs and introducing a drainage-tube." The reviewer contends that the incision must be made over the site of the circumscribed empyema, which may vary within wide limits among pulmonary invalids. Satisfactory drainage can rarely be secured by a simple incision between the ribs and the introduction of a tube. Dr Coleman says, "In some cases the space between the ribs is too narrow to admit a drainage tube of sufficient size. Then two or more ribs must be resected (Estlander's operation)." The reader should be informed that the resection of a single rib is usually sufficient for the purpose of simple evacuation and drainage, and that multiple rib resection is demanded for an entirely different purpose, i.e., the obliteration of the pus secreting cavity, this operation being indicated only after the lapse of many months. No mention is made of the aspiration of air in the valvular type of pneumothorax. The subject of rest and exercise is summarily dismissed by referring to the routine method employed at the Frimley Sanatorium. In the management of "Night Sweats," page 629, the author advises the use of "atropin as on the whole yielding the best results." Allusion is made in one and one-half lines to the employment of gelatin in the treatment of pulmonary hemorrhage. No explanation is given, however, as to the proper manner of its administration, and no caution as to the possibility of inducing tetanus. There appears no discrimination in the treatment of pulmonary hemorrhage according to the size or severity. The treatment of insomnia is very brief, relating largely to the administration of a few drugs. "Empiric" is misspelled, page 633.

Despite the instances cited, Dr Coleman's article is exceedingly interesting and contains much of value to the general practitioner.

The chapter on "The Sanatorium" is written by the editor. The article on "The Selection of the Sanatorium Site" is pertinent, and of value to those interested in the construction of these institutions. The author is unfortunate in the use of the relative pronoun ("The numerous sick which," page 642).

The article on "Physiology of Climate," by Dr Henry Sewell is scholarly scientific and of marked value. There is shown a commendable familiarity with the literature of the subject and a well poised understanding of the various problems discussed.

In the excellent chapter on "Climatic Therapeutics," Dr Barlow deals with the historical aspects of climate, enumerates the principal types, discusses the general utilization of climatic treatment in open and closed resorts, and then proceeds to a review of resorts. His description of the different regions is perfectly fair.

The several chapters on "Surgical Tuberculosis" by Dr Leonard Freeman and Dr L L McArthur are of much interest and exceedingly well written. In view of the importance of the subject and the limited space permitted to present a consideration of the surgical complications the writers are to be congratulated on the conciseness of their articles. The newer surgical procedures designed for the relief of pulmonary invalids are not discussed.

Owing to the large number of contributors and the varying merits of the different chapters it is extremely difficult to characterize adequately the production as a whole. Generalizing statements are obviously unfair, and therefore in justice to all it has seemed best to review the book by separate chapters. Despite a poor arrangement, important omissions, a few inconsistencies and contradictions, the absence of unity of thought, the character of the illustrations, and the many instances of incorrect grammatical construction, the book contains a fund of valuable information. That so many inaccuracies of expression should be overlooked by the editor is quite reprehensible. Inasmuch as the volume represents a series of very interesting articles by men eminently qualified to discuss the various phases of tuberculosis the reviewer commends it as a desirable addition to the literature on the subject.

## INFLAMMATION\*

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NEW YORK

The obvious causal relationship of bacterial infection to inflammation has tended to obscure the broader significance of the inflammatory reaction. An immense number of sterile substances, both fluid and solid, soluble and insoluble, organic and inorganic, incite a reaction which differs in no essential respect from that which follows the invasion of micro-organisms. Even so-called physiological salt solution introduced into the body may cause acute inflammation; absorption of a protein such as egg albumin or of a fatty substance such as sterile olive-oil is in part dependent on the same process. Views concerning the nature of inflammation are widely diverse, but all are agreed that inflammation accomplishes the destruction and solution of a variety of substances, and notably of those proteins which form the bodies of parasitic invaders.

Although absorption from the tissue, so-called parenteral resorption, is made possible by processes which resemble those occurring within the digestive tract, recent compendiums of biochemistry are almost silent concerning the nature of such processes and limit their discussion to a consideration of the part of filtration, osmosis, and the secreting activity of lining membranes. The pathological problems are unfamiliar to the physiological chemist, and the pathologist is poorly prepared to solve them.

It is well known that there is no agreement on what shall be regarded as inflammation, and some have wished to discard the word. I shall cite historical data with the sole purpose of showing that its historical associations offer little aid in determining its application, that accepted usage furnishes no more definite criterion.

The cardinal symptoms of inflammation—heat, pain, redness and swelling—described by the classical writers, have reference to inflammatory conditions affecting the surfaces of the body, perhaps well illustrated by erysipelas or by a boil. By a series of analogies the term has been applied to changes in the internal organs which exhibit, in some instances, none of these symptoms. Virchow, in the “Cellular Pathology,” shows that each one of the cardinal symptoms at some period has been used as a test of the true nature of inflammation. The name, which implies tak-

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\* Presented before the Harvey Society, New York, Feb. 19, 1910.

ing fire, shows that the early writers attached greatest significance to the increased heat of the inflamed part. At a later period, the condition of the blood-vessels indicated by congestion and redness, attracted more attention, and Boerhaave taught that inflammation was the result of stasis caused by obstruction of blood-vessels. This view prevailed during the period when, in France, pathological anatomy was studied with greatest industry. Ponfick cites the aphorism of Cruveilhier "Phlebitis dominates pathology." Yet Cruveilhier defines inflammation as a blood-stasis in the capillaries which is associated with exudation at times of coagulable lymph, at times of pus, perhaps finally, of caseous or tuberculous substance. As a criterion of inflammation, accumulation of exudate received increased attention, and the swelling or tumor of inflammation held a predominant place in the views of Rokitansky.

The experimental studies of Cohnheim inaugurate modern views on the nature of inflammation. Inflammation is the reaction which follows an injury affecting the wall of blood-vessels, increased permeability facilitates the escape of plasma and corpuscles into the surrounding tissue. Attempts to study the effect of various injurious substances upon a tissue devoid of blood-vessels, such as the cornea, have shown that well-known inflammatory changes occur in the adjacent vascular tissues and hence flood the injured part with exuded fluid and corpuscles.

Most of the substances which act as inflammatory irritants cause obvious injury to tissues with which they come into contact. At first sight it may appear unimportant to decide whether injury to tissue, including its blood-vessel, is the stimulus which puts in motion the numerous processes grouped as inflammation, or if the irritant itself acts directly on the structures with which it is in contact, and attracts to itself elements of the blood or of the tissues capable of neutralizing or destroying its toxicity. The decision will modify any interpretation of the phenomena of inflammation. One group of writers who have regarded injury to tissues as the inciting cause of inflammation, have included within its domain all those phenomena which tend to restore to normal the injured part, formation of fibrous tissue replacing elements which have been destroyed becomes a part of the inflammatory reaction. Inflammation is regarded as a process adapted to diminish the harmful consequences of an injury. This is the view expressed by the well-known definition of Burdon Sanderson, it represents the opinion maintained by Cohnheim, Weigert, Ziegler, Neumann, Letulle, Adam. Another group of writers, including Leber, Metchnikoff, Maichand, Ribbert, Councilman, Klemensiewicz, regard inflammation as a reaction excited by the presence of something injurious to the tissues, inflamma-

tion is adapted to counteract and destroy the injurious substance. Study of the phenomena by which bacteria are destroyed and dissolved has given this view a predominant place.

All inflammatory irritants produce some form of injury, and moreover, tissue which has been destroyed may act as an inflammatory irritant, nevertheless, there is a fundamental distinction between a reaction which repairs an injury, and reaction which renders harmless an injurious substance. Certain invertebrates with simple structure (*hydra*, *planaria*) repair an injury by rapid regeneration of a part removed, phenomena suggesting an inflammatory reaction are wholly lacking. Those who believe that inflammation is adapted to neutralize and destroy the injurious body usually exclude those regenerative changes which replace with fibrous tissue structures which have been destroyed, for all writers agree in excluding the regeneration which affects the surviving parenchyma when part of an organ has been removed or destroyed.

To determine if inflammation is dependent on changes in the blood-vessels attempts were long made to study the process in tissues such as the cornea or cartilage, which contain no vessels. The nearest vascular tissue became inflamed and the attempt failed. Directing his attention from the vertebrates which had heretofore served as objects of experiment to the lowest invertebrates, Metchnikoff has found the long-sought opportunity to study inflammation in tissues containing no blood-vessels. His well-known treatise on the comparative pathology of inflammation defines the relatively simple reaction which follows application of injurious agents to such animals.

Throughout the animal kingdom methods used to obtain food are often employed to destroy enemies. The ameba survives because it can destroy and digest the bacteria which it takes into its substance. In certain sponges, phagocytic cells, which digest the food of the animal, accumulate about a foreign body thrust into its substance. The lower orders of invertebrates, such as the medusa, the starfish and certain worms possess no vascular system, situated between the outer covering and the digestive cavity are mesodermic cells which, having no part in the digestion of food, approach, engulf and often digest foreign particles, bacteria and other organisms which have found their way into the tissues of the animal. By means of ameboid movement they accumulate about any substance capable of exciting their activity. Shall this reactive accumulation of phagocytic cells be designated "inflammation"? Those who believe that inflammation is a response of blood-vessels to injurious agencies are unwilling to include it. With a broader view, those processes by which protective elements are drawn from adjacent tissues cannot be

separated from those changes by which similar cells are drawn from adjacent blood-vessels. Nomenclature of the process is relatively unimportant. Yet study of what is universally designated "inflammation" in animals with fully developed blood-vessels shows that phagocytic cells which react in response to the inflammatory irritant are not necessarily derived from the blood-vessels.

To illustrate the chaotic state of prevailing views concerning inflammation, the status of tuberculosis may be cited. Cohnheim, who attached prime importance to vascular changes, excluded the infectious granulomata, yet many of those who believe that inflammation occurs only in vascular tissue regard tuberculosis as inflammation. Marchand, on the contrary, separates such processes from inflammation, because he believes that they are characterized by multiplication of fixed cells of the tissue.

Inconsistencies of accepted nomenclature are readily found. The term, parenchymatous nephritis, a survival of Virchow's conception of inflammation now long abandoned, is applied to a lesion which exhibits none of the vascular and cellular changes which are associated with inflammation of other organs. Injury to the spinal cord is designated as inflammation when it is called traumatic myelitis, yet the secondary occurrence of inflammatory changes common to all forms of injury merely serves to emphasize the confusion of two distinguishable conditions (Marchand<sup>1</sup>). The name "acute hemorrhagic pancreatitis" has been applied to a lesion which is essentially necrosis, and not inflammation of the pancreas, and its use has hindered a rational classification of pancreatic disease.

Should we assume that inflammation occurs in order that injurious substances may be destroyed or removed, the nature and action of the fluid and cells which accumulate acquire predominant importance. The swelling of inflammation is in great part referable to accumulation of fluid derived from the plasma of the blood, yet the wall of the vessel controls this transit, for the protein content of the fluid which passes through the wall of the blood-vessel into the tissue is constantly less than that of the blood plasma. The proteins of the plasma do not enter the spinal fluid nor the aqueous humor, yet with inflammation they are found in both fluids.

Studies of Klemensiewicz<sup>2</sup> have shown the effect of increased pressure exerted by exudate within the tissue on local vascular tension. By an ingenious device he has been able to measure directly under the microscope the pressure capable of producing stasis within the capillaries. When an

1 Marchand Ueber die natürlichen Schutzmittel des Organismus, Leipzig, 1900

2 Klemensiewicz Entzündung, Jena, 1908

Inflammatory irritant is applied to the tissue under examination, accumulation of exudate increases extravascular tension, and a smaller pressure is now capable of causing capillary stasis. This observation may help to explain the obvious truth that accumulation of fluid in the subcutaneous tissue in response to an irritant, is quickly self-limited, whereas the same irritant causes an immense serous exudate when introduced into a serous cavity. Later it will be shown that this difference has an important influence on the outcome of the inflammatory reaction and may determine whether suppuration or resolution occurs.

During the last ten years an immense amount of laborious study has been devoted to the character and origin of the various cells which accumulate at the site of inflammation. The studies of Cohnheim and of von Recklinghausen have afforded convincing evidence that the common pus corpuscle is the polynuclear leucocyte of the blood which, under the stimulus of the inflammatory irritant, passes through the walls of blood-vessels. Some of the earlier observers have believed that such polynuclear leucocytes may become cells of the fixed tissue, colonize the part, as it were, but there is now universal agreement in the view that they may degenerate but undergo no progressive transformation after they have left the blood-stream. The origin and fate of the numerous mononuclear cells which accumulate in the inflamed tissue on the contrary is doubtful. The subject, repeatedly investigated by histological methods, often uninteresting because they are inconclusive, has great biological importance, for it deals with the significance of lymphatic tissue and the normal and pathological relationship between lymphatic and other tissues of the body. It seeks to determine if a cell formed in one part of the body may establish itself in a distant part and there form an integral constituent of the tissue.

Insight into the changes associated with inflammation assumes an accurate knowledge concerning the tissue in which the inflammatory reaction occurs. All of these changes have their origin within the connective tissues of the body whence inflammatory exudates may find their way into other situations. There are yet many defects in knowledge of the connective tissues of the body. In early stages of embryonic life this tissue is represented by a network of cells with branching processes which are continuous with one another. Within the substance of this protoplasmic syncytium, and hence within the cells, according to observations of Fleming, and in recent years of Mall,<sup>3</sup> the white fibers are laid down. At first all the cells which compose this tissue are fixed, but later cells make their appearance within the meshes of the network. Since these unattached cells exhibit irregular projections which suggest that they are

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<sup>3</sup> Mall Am Jour Anat., 1902, 1, 329

capable of ameboid movement, and since they resemble ameboid cells of the circulating blood, they are regarded as wandering cells. Part of them have all the characters of lymphocytes and in many situations form small collections about the blood-vessels. Part of them are larger than lymphocytes and resemble the large mononuclear cells of the blood, they are frequently collected about blood-vessels.

Von Recklinghausen has maintained the opinion that the spaces which, filled with fluid, exist in the meshes of the network formed by the fixed elements of the tissue, are in direct communication with lymphatic capillaries and constitute the origin of the lymphatics within the tissue. Nearly half a century ago (according to Sabin) Langer showed that these lymphatics grow as blind sprouts of endothelial cells. Ranvier has confirmed this almost forgotten observation in recent years, and Sabin<sup>4</sup> and others have shown that the entire lymphatic system sprouts from the endothelial lining of veins and gradually pushes its way into various tissues and organs to form a closed system everywhere lined by endothelial cells. Endothelium separates the lymph within the lymphatic capillaries from fixed cells of a part. This well-known relationship, usually little considered, has much pathological significance, indeed early observers (Hering, Heller, Thoma<sup>5</sup>) of the movements of ameboid cells within the tissues, have noted the important truth that leucocytes which have wandered from the wall of the blood-vessels and have passed through the spaces within the fixed tissue, may penetrate the endothelial wall of a lymphatic vessel.

Embryological study of the lymphatic nodes has explained the relationship of lymphatic tissue to lymphatic vessels. Gulland,<sup>6</sup> Sabin<sup>7</sup> and others have shown that lymphoid tissue makes its appearance in the walls of lymphatic channels which have already been formed, and consequently a layer of endothelial cells separates the lymphatic tissue from the lumen of the lymphatic vessel, and later from the tortuous sinus to which the primitive channel gives place. The lymphocytes of the lymph-node appear within the meshes of a fibrillated network and in their relation to lymphatics are analogous to the lymphocytes in the meshes of connective tissue elsewhere.

The local changes which with inflammation occur in the lymphatic vessels of the affected part and in the tributary lymphatic nodes (see diagram) are not separable from the changes which have their seat in

<sup>4</sup> Sabin Anat Rec, 1908, II, 46

<sup>5</sup> Thoma Text-book of General Pathology (Transl.), London, 1896, p 330

<sup>6</sup> Gulland Jour Path and Bacteriol, 1894, II, 447

<sup>7</sup> Sabin Am Jour Anat, 1905, IV, 355

the blood-vessels and in the interstitial tissue Muscatello<sup>8</sup> has shown that finely granular material, such as carmine powder, introduced into the peritoneal cavity of a dog, appears within ten minutes in the retrosternal lymphatic nodes, the two retrosternal lymphatic channels which follow the internal mammary arteries are quickly rendered conspicuous by the injected material. Within these lymphatic vessels some of the granules are free in the lymph, whereas others are contained in wandering phagocytic cells which, as MacCallum<sup>9</sup> has shown, penetrate the endothelial lining of the diaphragm. Within three-quarters of an hour after injection of *Staphylococcus aureus* into the subcutaneous tissue of the leg of a guinea-pig, Bezançon and Labbé<sup>10</sup> found that the afferent lymphatic vessels of the adjacent lymphatic node were dilated and

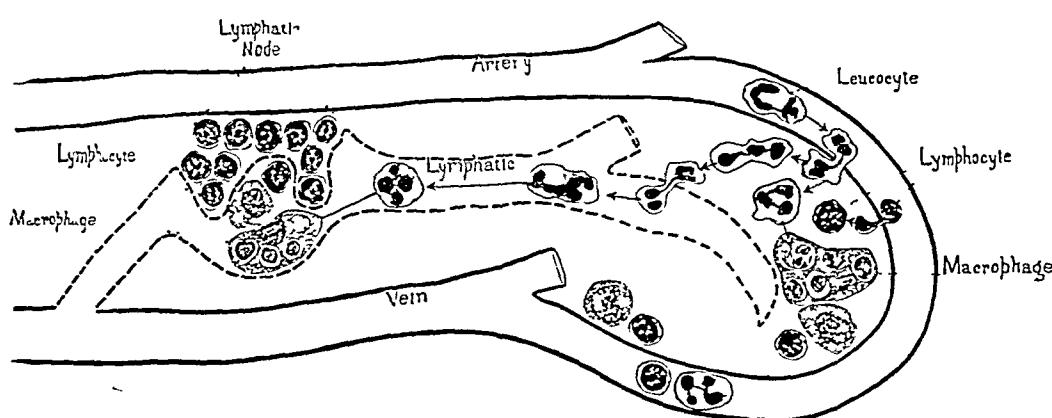


Diagram showing the relation of the site of inflammation to the regional lymphatic node. An artery is shown dividing to form a capillary which in turn enters a vein, within the capillary loop is a lymphatic vessel which becomes the sinus of the adjacent node and finally discharges its contents into the venous system. Within the capillary loop to the left of the dotted line is shown the normal position of wandering cells. To the right of the dotted line are shown cells having part in the inflammatory reaction. Polynuclear leucocytes which migrate from the blood-vessels may be ingested by macrophages or may enter the lymphatic, pass to the adjacent lymphatic node and perhaps undergo ingestion by a macrophage within the sinus of the node. The data on which the diagram is based are described in the text.

contained many polynuclear leucocytes which were entering the sinuses of the node. The subsequent changes within the node are well known.

The well-known studies of Maximow<sup>11</sup> have defined the changes which occur in and about a sterile foreign body, introduced into the subcutane-

8 Muscatello Virchow's Arch f path Anat, 1895, exlii, 327

9 MacCallum Bull Johns Hopkins Hosp, 1903, viii, 105

10 Bezançon and Labbé Arch de méd expér, 1898, x, 318

11 Maximow Beitr z path Anat u z allg Path (Ziegler's) 1902, v, suppl, 1, 1905, xxxviii, 301

ous tissue of various species of animals. In later experiments he has impregnated the body with an inflammatory irritant such as turpentine, or has infected it with pyogenic bacteria, namely, with *Staphylococcus aureus* and with *streptococcus*. He has pictured with great clearness the changes observable at intervals varying from a few minutes to many days after onset on the inflammatory reaction. The reaction caused by a sterile body differs from that produced by bacteria in its intensity and in the rapidity with which corresponding phenomena occur, but the character and sequence of events are identical.

Serous fluid quickly accumulates about the infected body and the surrounding tissues become edematous. Within the first four hours poly-nuclear leucocytes emigrate from the blood-vessels in large numbers, and properly prepared tissue exhibits many leucocytes making their way through the endothelial lining of vessels. Early emigration of lymphocytes as well has so frequently been observed that its occurrence has been placed beyond doubt. The small round cells which migrate from the blood vessels quickly give place to larger cells with paler, larger nucleus and fairly abundant cell substance. Those cells which have a predominant part in the late stages of inflammation are known by no familiar name, and it is difficult to designate them conveniently. The term "macrophage," used by Metchnikoff, is applicable, for these cells exhibit phagocytic activity, but the name has a wide significance and may be applied to all large cells capable of ingesting solid particles. The attack on living virulent micrococci is apparently conducted wholly by polynuclear leucocytes. With the disappearance of micrococci, mononuclear cells increase in number and in size and begin to exhibit ability to ingest cells and cellular debris. Such phagocytic cells or macrophages may contain six, a dozen or more leucocytes in various stages of disintegration, together with a variety of inclusions whose origin is no longer recognizable. On the activity of these cells is in large part dependent the solution and removal of the leucocytes which have previously attacked the invading bacteria.

The serous cavities, particularly the peritoneal and pleural cavities, offer a convenient opportunity for study of the cellular phenomena of inflammation. The early changes, whether produced by various bacteria or by sterile irritants, do not differ materially. A noteworthy peculiarity of inflammation within serous cavities is the unobstructed and rapid accumulation of serum, the cells which accumulate are in part suspended in this fluid but a greater part adhere to the membranes, such as the omentum or mediastinum which are contiguous with the cavity. Numerous observations have shown that the changes which occur in the serous cavity

during the first few hours after inoculation are identical with those which are demonstrable under similar conditions in the subcutaneous tissue

The importance of vascular changes in inflammation has long been recognized, less has been written concerning the significance of the lymphatic system. The studies which have been cited show that the lymphocytes which are in great part at least derived from the lymphatic glands migrate from the blood-vessels and are perhaps transformed into macrophages. At the same time lymphocytes and similar larger cells which are scattered in the normal tissue outside of the blood-vessels and often according to Ribbert form rudimentary lymphatic nodes mingle with the cells of the exudate and perhaps take part in the formation of macrophages. The intimate relationship of the local focus of inflammation to the adjacent lymphatic glands is well illustrated by the experimental pleurisy produced by injection of a sterile irritant such as the vegetable protein, aleuronat, into the pleural cavity. The lymphatic glands which are situated in the anterior mediastinum become greatly swollen and microscopic examination shows that changes which occur in the sinuses of these glands are identical with those in progress within the pleural cavity itself. At the end of four or five days the serous cavity contains abundant fluid in which polynuclear leucocytes are abundant, at this time mono-nuclear phagocytic cells are large and numerous and are engaged in ingesting and dissolving polynuclear leucocytes. The sinuses to the adjacent mediastinal lymphatic glands are much distended and closely packed with the same large phagocytic cells whose protoplasm often contains many polynuclear leucocytes in various stages of disintegration. In some instances almost the entire lymphatic gland is replaced by these cells. Ingestion of polynuclear leucocytes and other cells, essential to complete resolution of the exudate, is begun in the serous cavity and is completed in the regional lymphatic node. By the method previously described cells make their way along lymphatic channels from the primary site of inflammation to the adjacent node.

Studies of the fate of bacteria injected into the body have demonstrated the rapidity with which micro-organisms enter the regional lymphatic nodes, and the partial efficiency of these nodes as filters. Buxton and Torrey<sup>12</sup> have injected typhoid bacilli in considerable quantity into the peritoneal cavity of small animals and have estimated by the enumeration of colonies in agar plates the relative abundance of bacteria in the substernal lymphatic nodes, in the blood and in various organs such as the liver, spleen, lungs, bone-marrow and kidney. Within ten minutes after inoculation, they found an enormous number of bacteria in plates

12 Buxton and Torrey Jour Med Research, 1906, xiv, 213 1907 xvi, 17, 251

prepared from the regional lymphatic node, and in sections prepared for microscopic examination bacilli are found in the afferent sinus, in part free, in part within phagocytic cells. Notwithstanding this regional fixation of those bacteria which had escaped from the site of inoculation, a not inconsiderable number had entered the blood and were scattered throughout the body. Within the interval from five to thirty minutes after inoculation, from twenty to thirty thousand bacteria per cubic centimeter were recovered from the blood. Nevertheless at the end of an hour, the number had fallen to several hundred. Likewise within the first half hour after inoculation the number of bacteria in the liver, spleen, lungs and kidney was very great, but it fell suddenly and soon became relatively small. This initial rush of bacteria from the peritoneal cavity to the blood has been found to occur with equal readiness in normal and in immunized animals.

Experiments of Muscatello have shown that inanimate particles such as powdered carmine pass through the diaphragm into the lymphatic vessels of the mediastinum and reach the circulating blood only through the lymphatic system. Wells and Johnstone<sup>13</sup> have successfully attempted to show that bacteria do not pass into the blood-vessels of the peritoneum but reach the blood wholly by way of the lymphatic vessels. They have prevented the initial rush of bacteria from the peritoneal cavity into the blood by ligation of the thoracic duct. By estimation of the number of bacteria in the lymph they have shown that the thoracic duct, during the first hour after inoculation of the peritoneal cavity with *Bacillus coli* discharges an immense number of bacteria into the blood.

The foregoing observations show that the lymphatic nodes, during the first hour after inoculation, are not efficient filters for bacteria. Although two lining membranes are interposed between the peritoneal cavity and the interior of lymphatic vessels, solid particles pass with the utmost rapidity from one to the other, the greater part of these particles are not contained within phagocytic cells. The membranes separating the cavity and the lumen of the vessel are uninterrupted but solid particles pass as if there were direct communication. Furthermore, both bacteria and inanimate particles at first pass the lymphatic nodes, but later at the end of the first half hour or hour after inoculation, although the peritoneal cavity and the regional lymphatic nodes contain an immense number of bacteria, their escape is obstructed and they have almost completely ceased to enter the circulating blood. At this time an inflammatory reaction has begun both at the site of infection and within the lymphatic node. There is little doubt that the quiescent lymphatic node

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13 Wells and Johnstone Jour Infect Dis, 1907, iv, 582

is an inefficient filter whereas the inflamed node containing even at this early period, many phagocytic cells, is effective in restraining the dissemination of bacteria.

Noetzel<sup>14</sup> injected *Bacillus pyocyaneus* into the knee-joint of rabbits, and from five to ten minutes later found the organism both in the inguinal, lumbar and crural lymphatic nodes and in the circulating blood. Pawlowsky<sup>15</sup> has demonstrated the presence of staphylococci in the blood and organs of guinea-pigs from twenty-four to forty-eight hours after inoculation of the knee-joint, but has been able to show that this dissemination is inhibited or wholly prevented if before inoculation, acute inflammation of the joint has been produced by the injection of some sterile irritant such as turpentine, alcohol or solution of quinin. His observation recalls the studies of Issayeff, who showed that the peritonitis induced by a variety of sterile irritants such as foreign blood-serum, bouillon or normal salt solution, temporarily increases resistance to subsequent intraperitoneal inoculation of bacteria. Such observations help to explain the well-known resistance to infection exhibited by a granulating wound.

A great variety of substances which are either non-dialyzable or insoluble in water are dissolved and removed when introduced into the tissues of an animal. It is difficult, perhaps impossible, to cite any substance which introduced from outside of the body into the tissues of an animal fails to excite an inflammatory reaction, physiological salt solution introduced into the peritoneal cavity produces active emigration of leucocytes. Comparatively little systematic observation has been made on the pharmacology of inflammation and we are as yet ignorant of the factors on which depend peculiarities in the intensity of the reaction and in the character of the exudate which is produced. The reaction is in all instances characterized (a) by a stage of leucocytic emigration followed when resorption begins, (b) by accumulation of macrophages. It is noteworthy that tubercle bacilli and typhoid bacilli, whose presence in man is usually associated with peculiar lesions exhibiting little resemblance to acute inflammation, produce the same changes during the first twenty-four hours after introduction as *Staphylococcus aureus* (Helly) and other pyogenic cocci.

Nevertheless one large group of substances, unlike bacteria, excite the large mononuclear phagocytes with much greater activity than poly-nuclear leucocytes. The cells of one animal introduced into the body of another of the same or of a different species are attacked by large mono-

14 Noetzel Beitr z klin Chir, 1906, II, 740

15 Pawlowsky Ztschr g Hyg, 1909, lxii, 433

nuclear cells and are gradually dissolved within their substance. This experiment has been repeated under a great variety of conditions by Metchnikoff and his pupils. The same process occurs under physiological conditions, for in the spleen red blood corpuscles, perhaps those which have undergone some degenerative change and are no longer useful to the body, are ingested and destroyed by large mononuclear phagocytes. When hemorrhage occurs into the tissues, phagocytic cells of similar character, by taking red corpuscles into their substance, aid in the process of absorption. Necrotic tissue in the liver or in other organs is absorbed by aid of the same cells. A similar process occurs when degenerative changes affect the central nervous system. Absorption of tissues no longer useful to the body, and perhaps already the seat of degenerative change, is accomplished by the aid of mononuclear phagocytes and has many analogies throughout the animal kingdom. Metalnikoff, studying the progress of the metamorphosis of insects, has lately found evidence that the organs and tissues first undergo degenerative changes, and later become the prey of phagocytes. Furthermore, one large group of parasitic invaders, including protozoan micro-organisms such as malarial parasites and trypanosomes, excite almost exclusively the activity of the mononuclear phagocytes.

The observations which have been cited show what cells accumulate about a foreign substance introduced into the body. The more important of these cells are capable of engulfing solid protein particles, and of dissolving them. By what means is this absorption accomplished?

The occurrence of products of protein digestion in inflammatory exudates was recognized almost fifty years ago. Eichwald in 1864 found in pus what was then called peptone, and later, Maixner found peptone in the urine in association with a considerable variety of suppurative conditions such as empyema, peritonitis, cerebrospinal meningitis, pyelitis, etc. An observation of Friedrich Muller has explained the constant presence of so-called peptone in purulent phthisical sputum, a glycerin extract of such sputum is capable of digesting fibrin or coagulated albumin in a weakly alkaline medium. Other purulent sputum has the same property, the sputum of a patient with pneumonia does not exhibit this digestive action before crisis has occurred, but later when it has assumed a white pus-like appearance, the enzyme may be demonstrated. The pus of an abscess contains the same enzyme, but the pus-like fluid from a tuberculous lesion, a so-called cold abscess, fails to contain it. Various observers have shown that enzyme of pus is capable of digesting a considerable variety of protein substances, such as gelatin, fibrin, coagulated egg albumen and casein. The well-known studies of Salkowski first showed

that animal tissues preserved under conditions which prevent the growth of bacteria undergo changes similar to those which occur during the digestion of protein. Friedrich Muller showed that the pneumonic lung consolidated by the presence of inflammatory exudate within the alveoli, is especially susceptible to such autolysis. By the self-digestion of this inflamed pulmonary tissue at body temperature are formed albumose, leucin, tyrosin and other products of protein disintegration, nuclei of the autolyzed tissue quickly disappear as a result of decomposition of nucleins. These observations have been used to explain the solution of fibrin and the disappearance of leucocytes and other cellular elements which occurs with resolution of the exudate.

Biondi,<sup>16</sup> Hedin and Rowland,<sup>17</sup> and others have found that various normal organs of the body autolyze with greater activity in weakly acid than in alkaline solutions, and in this respect resemble pepsin rather than trypsin.

Studying the cells of an inflammatory exudate obtained by injection of aleuronat or other sterile irritant, I have repeatedly confirmed the observation that they digest coagulated protein with greatest activity when they are suspended in an alkaline medium. Digestion may be accurately measured by allowing the cells to act at body temperature on blood-serum coagulated by heat, the amount of protein which goes into solution may be accurately determined. Testing the liver, kidney, spleen, lymphatic node, and bone marrow, it is noteworthy<sup>18</sup> that the bone-marrow alone resembles the cells of an acute inflammatory exudate, and digests with greater activity in alkali than in acid.

The cell which is predominant in the inflammatory exudate produced by the injection of aleuronat is the polynuclear leucocyte, and histologists are agreed that this cell has its origin in the bone-marrow. In other words, polynuclear leucocytes which, constituting the greater part of the white corpuscles of the blood, migrate during the early stage of the inflammatory reaction, and approach and digest solid particles, contain an enzyme which resembles trypsin of the pancreas. They carry this enzyme from the bone-marrow to the site of inflammation. Dochez has shown that this enzyme, unlike trypsin, exists within the cells in an active state, and will, without further change, act on protein in the presence of alkali. Trypsin, on the contrary, exists in the pancreatic cells as zymogen, and requires activation by enterokinase or by acid before it is able to attack protein.

16 Biondi. *Vnichow's Arch f path Anat.*, 1896, cxliv, 373.

17 Hedin and Rowland. *Ztschr f physiol Chem.*, 1901, xxxii, 341.

18 Opie. *Jour Exper Med.*, 1905, vii, 759.

The enzyme of the polynuclear leucocytes, which may be conveniently designated "leucoprotease," may be purified by precipitation with alcohol, and after drying may be preserved almost indefinitely<sup>19</sup>. In the moist state, the enzyme thus prepared is destroyed by heating at a temperature between 70 and 75 C. Temperatures between 50 and 65 C acting on the enzyme during half an hour increase its activity. It acts in an alkaline or in a neutral medium, but is inhibited by acid. Sodium carbonate in concentration of 0.2 to 0.5 per cent favors its action, greater concentration is destructive. The enzyme is much less active than trypsin, but it is not improbable that its activity, tested outside the body, is less than its activity under the favorable conditions which doubtless exist within the leucocyte.

Examination of the properties of the enzyme which has been described, demonstrates that it is not identical, as several writers have claimed, with the alexin or complement of the blood-serum, for the latter, it is well known, is destroyed by heating to a temperature of 56 C. Jochmann<sup>20</sup> has shown that it has no bactericidal power and asserts that it digests bacteria which have been killed by chloroform or by heat, whereas it fails to dissolve living bacteria.

It is not difficult to bring proof<sup>20</sup> that the cells which accumulate in response to the presence of an inflammatory irritant contain a second enzyme capable of digesting albuminous substances, its properties are different from those peculiar to the enzyme of the polynuclear leucocytes. The enzyme which is obtained by treating the cells with alcohol, it has been mentioned, acts in both neutral and alkaline solutions, but is inactive in acid, the fresh cells, however, digest in acid as well as in alkali. This observation suggests that alcohol destroys a second enzyme, present in the fresh cells. Further study has shown that this second enzyme is more labile than leucoprotease, for whereas temporary heating to temperatures between 50 and 65 C increases the activity of leucoprotease, it greatly diminishes the activity of the enzyme which digests in the presence of acid.

I have previously cited many observations which show that two types of cells are abundant in all inflammatory exudates which exhibit a tendency to resolve. When aleuronat is injected into the pleural cavity of a dog the proportion of large mononuclear cells, which act as phagocytes, gradually increases and with this increase there is increasing power to digest in the presence of acid. I have already pointed out that the phagocytosis of micro-organisms, foreign particles, polynuclear leucocytes, red

19 Opie Jour Exper Med, 1905, vii, 316, 1906, viii, 410

20 Jochmann Ztschr f Hyg, 1908, lxi, 71

blood corpuscles, and cellular débris begun in the pleural cavity is completed in the regional lymphatic nodes. At the end of four or five days after the onset of inflammation incited by aleuronat the retrosternal lymphatic nodes are enormously enlarged beyond their normal size and their sinuses are distended with large cells identical with those in the pleural cavity and actively engaged in the phagocytosis of polynuclear leucocytes and other cellular elements. An emulsion prepared from such a lymphatic node in which mononuclear phagocytes are predominant, fails to digest protein in an alkaline or neutral medium but exhibits active proteolysis in the presence of acid. Moreover, this form of enzymatic activity increases with the duration of the changes in the node. The regional lymphatic node contains in almost pure form that enzyme which in the exudate increases with the increased number of macrophages. I have suggested for this enzyme the name "lymphoprotease."

This enzyme, like pepsin, acts in an acid medium and is inhibited by alkali, but it is not identical with pepsin, for it acts with greatest activity in a very weak concentration of hydrochloric acid and is destroyed by that strength (0.2 per cent) which is favorable to the action of pepsin. It is more closely related to the autolytic enzyme of various tissues. The factor of essential importance is the increase of this enzyme which is associated with an increase of large mononuclear phagocytes in the exudate or with an increase of similar cells in the lymphatic nodes tributary to the inflamed area.

The enzymes which have been found in the cells of the serous inflammatory exudate just described are present as well in fibrinous exudates.<sup>21</sup> When a small quantity of turpentine is injected into the pleural cavity, coagulable fluid accumulates and reaches a maximum at the end of two or three days. The exuded fibrin, which contains polynuclear leucocytes during the first three or four days of inflammation, undergoes solution when suspended in an alkaline medium, whereas at a later period when polynuclear leucocytes have disappeared, this property is lost. On the second or third day after onset of the inflammatory reaction, products of proteolytic digestion appear in the serum, reactions indicating the presence of albumose are readily obtained. Such decomposition products are doubtless absorbed with great rapidity, for large quantities artificially introduced disappear from the exudate within twenty-four hours.

Although leucocytes contain active enzymes, serous inflammatory exudates containing cells in abundance fail to undergo autolysis. Experiments which I made several years ago have explained the absence of such autolysis and have disclosed a mechanism by which the activity of the

21 Opie Jour Exper Med., 1907, ix, 391, 414

enzyme is limited to the locality in which it is needed. The cells of the exudate separated from the serum undergo autolysis and are capable of digesting foreign protein, but if to the cells the exuded serum is added, digestion is wholly inhibited.

The serum contains some substance capable of restraining the action of the enzyme, it is convenient to designate this substance "antienzyme," without implying thereby that it is a specific antibody adapted to combine with enzyme in accordance with laws of chemical union. The antienzymotic action of the exuded serum is exhibited by the serum of the blood as well, it passes with the serum into the inflammatory exudate. The observation of E. Muller<sup>22</sup> that the antienzyme fails to enter the normal cerebrospinal fluid, has a considerable interest.

The antienzyme is destroyed by heating to 75° C. It is apparently attached to the albumin fraction of the serum for the globulin exhibits no antienzymotic action, whereas the albumin fraction is active. The antiaction occurs in an alkaline or neutral medium, but is destroyed by acid. The phenomenon can be accurately studied by adding to weighed quantities of leucoprotease different volumes of serum. Such experiments do not afford evidence that enzyme and antienzyme combine in definite quantities. Nevertheless, if to a fixed quantity of serum, increasing quantities of enzyme are added, a point is reached at which the serum fails to restrain completely the activity of the enzyme. In the study of suppuration this observation has considerable importance.

Antienzymes in the blood serum similar to that which restrains the action of leucoprotease have long been known. Hahn in 1897 showed that the blood-serum inhibits the action of trypsin. It is not improbable that the inhibitory effect on trypsin and on leucoprotease are dependent upon some peculiarity of the same substance, for Jochmann and Kantorowicz<sup>23</sup> have found that blood-serum which has abnormally high antitryptic action exhibits an increased ability to restrain the action of leucoprotease. Furthermore, there is no specific relationship between the enzyme of one species and the antienzyme of the same species, the serum of the rabbit has greater antienzymotic action on dogs' enzyme than dogs' own serum.<sup>24</sup> Birds' serum unlike mammalian serum, fails to inhibit leucoprotease, which is peculiar to mammals.

The relationship between leucoprotease and its antienzyme in the serum furnishes a mechanism by which the action of the enzyme is limited to the locality in which it accomplishes its function. The polynu-

<sup>22</sup> Muller, E. Munchen med Wehnschr., 1907, I, 354

<sup>23</sup> Jochmann and Kantorowicz Zeit f klin Med., 1908, LVI, 153

<sup>24</sup> Opie and Barker Jour Exper Med., 1907, II, 207

clear leucocyte is suspended in a fluid which neutralizes the effect of its enzyme, should this enzyme be set free by disintegration of the cell or by other means. When the polynuclear leucocyte ingests a solid particle of protein matter, for example, a bacterium, it removes it from contact with the serum and brings it into contact with its enzyme.

The mononuclear phagocytes are subject to a similar influence, for numerous experiments have shown that the enzyme which they contain is restrained by the serum of the blood, and similarly by the serum of an inflammatory exudate. In what degree this antienzymotic action depends on the apparent alkalinity of the serum, and in what degree on a thermolabile antibody, has not been established.

The relation between leucoprotease of the polynuclear leucocytes and the antienzyme of the serum has served to explain the essential nature of abscess formation. Ribbert<sup>25</sup> defines suppuration as follows: "It is an intense inflammation with which polynuclear leucocytes wander from the blood-vessels in unusually great quantity, the tissue is softened and the serum between the collected pus cells does not coagulate." It may be added that solution of tissue in some instances has a beneficial result, for softening of the least resistant tissues may result in superficial rupture with healing, without escape of pus, it is well known there is little tendency to heal.

The peculiar appearance of pus is in part dependent on the presence of a great quantity of pus cells suspended in a relatively small proportion of fluid. A serous or serofibrinous exudate, on the contrary, contains abundant fluid and a relatively small proportion of cellular elements. Whereas the serum of the serous or serofibrinous exudate inhibits the digestive action of leucoprotease, the serum obtained from pus not only fails to inhibit leucoprotease, but itself contains unrestrained enzyme.<sup>26</sup> By disintegration of leucocytes, doubtless referable to the inflammatory irritant, increasing quantities of leucoprotease have been set free so that the antienzymotic activity of the exuded serum is finally overcome. The proteolytic enzyme may now come into contact with tissue and with fibrin, and softening is the result.

The following experiment serves to explain why the same irritant in the same quantity may cause two different types of inflammation. If a small quantity of turpentine is injected into the subcutaneous tissue of a dog, a large fluctuating abscess filled with creamy pus is formed within four days, there is wide-spread undermining of the skin. The same quantity of turpentine injected into the pleural cavity causes a sero-

25 Ribbert. Lehrbuch der allgemeinen Pathologie, Leipsic, 1905, 367.

26 Opie. Jour. Exper. Med., 1906, viii, 536.

fibrinous inflammation which undergoes resolution so that the pleural cavity is restored to its normal condition after about ten days, there is no destruction of tissue and a scar is not formed. In the subcutaneous tissue only a small amount of edematous exudate can accumulate, the undiluted irritant causes active migration of leucocytes so that the antibody of the exuded serum is soon overbalanced by the enzyme set free by disintegrated pus cells. In the pleural cavity, on the contrary, a large quantity of serum quickly accumulates and the exudate is serofibrinous instead of purulent, the antienzyme it contains is capable of holding in check the leucoprotease of the accumulated leucocytes. If a bit of the fibrinous exudate is suspended in the exuded serum, it is preserved intact. Nevertheless, by repeated injection of turpentine at short intervals into the pleural cavity, accumulation of leucocytes may be prolonged so that finally a condition is produced in which antienzyme can no longer restrain the enzyme. The softened fibrin of such an exudate quickly disintegrates in the serum of the exudate.

The foregoing observation introduces a new factor into the discussion concerning the pyogenic activity of many bacteria. It helps to explain how the typhoid bacillus produces abscesses in certain situations such as the kidney and bone, how the pneumococcus, which rarely causes abscess of the lung, in which conditions are somewhat similar to those within the pleural cavity, may cause suppuration in other localities, such as the middle ear or in the subdural space, how the tubercle bacillus may, under peculiar conditions, cause true suppuration.

It is noteworthy that the normal spinal fluid, unlike other body fluids, contains neither enzyme nor antienzyme, and for this reason, Dochez<sup>27</sup> has made a special study of the changes which occur in association with inflammation. With epidemic meningitis, antienzyme may enter the spinal fluid and quickly leaves it. With more virulent infection caused by pneumococcus or streptococcus enzyme derived from disintegrated polynuclear leucocytes gives to the fluid well marked power to digest protein. Such active enzyme itself doubtless acts as an irritant and increases the severity of the disease.

A few writers, notably Maichand, exclude the infectious granulomata from the domain of inflammation, they are those who, on the one hand, accept the opinion of Baumgarten that the tubercle is formed from elements of the fixed tissue, and on the other hand, do not apply the term "inflammation" to regenerative changes in the fixed tissue. Nevertheless, the greater number of pathologists give weight to the truth that the tubercle is formed by a reaction in response to the presence of an invading

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27 Dochez Jour Exper Med., 1909, vi, 718

parasite, and this reaction, in its early stage, is identical in character with that which follows the entrance of other bacteria into the tissues. Tuberculous tissue, moreover, is composed in large part of so-called epithelioid cells, these cells have the anatomical structure and phagocytic activity of the large mononuclear cells which predominate in the later stages of an acute inflammatory reaction. With present knowledge, it is impossible to define clearly the relationship of the tubercle to the later stage of inflammation, for the available evidence has permitted no agreement concerning the origin of the epithelioid cells. Study of acute inflammations produced by a sterile foreign body or by bacteria demonstrates with considerable certainty that lymphoid cells leave the blood-vessels and, it is probable, assume the characters of macrophages. In the immense accumulation of cells which follows, the identity of various elements is lost and only the uncertain means of tracing transitions from one form to another is available for determining origin of various types. Large mononuclear cells are accumulating in the tuberculous and in the non-tuberculous inflammation after the first twenty-four hours. There is no doubt that small round cells with the character of lymphocytes accumulate in the neighboring blood-vessels and migrate from them during the formation of the tuberculous lesion. Though transitions from this lymphoid cell to epithelioid cells are not wanting, there is no convincing evidence that one is derived from the other.

Polynuclear leucocytes occur in scant number in tubercles found at autopsy, yet in man (Benda), as in other animals, they are the first cells to accumulate about tubercle bacilli which are free in the tissues. Within an hour after injection of tubercle bacilli into the blood or into a serous cavity, they are surrounded or ingested by polynuclear leucocytes, mononuclear cells subsequently appear. In some animals, polynuclear leucocytes are very numerous in tuberculous tissue. In the dog, during the first few weeks after inoculation of the pleural cavity, polynuclear leucocytes occur in immense numbers in the tuberculous tissue which is formed in and on the mediastinum. The relative abundance of these cells is dependent on the character of the bacillus, and in some degree is an index of the activity of resistance upon the part of the host. Virulent tubercle bacilli excite a more active emigration of polynuclear leucocytes than non-virulent organisms.

If the lesions which are classed as infectious granulomata are passed in review various conditions intermediate between the tubercle and a simple abscess are found. The actinomycotic nodule has many of the characters of the tubercle, yet polynuclear leucocytes are so abundant that a small abscess is formed in the immediate neighborhood of the micro-

organism Glanders, in man and in lower animals, is usually characterized by abundant accumulation of polynuclear leucocytes with necrosis and suppuration Duval and White<sup>28</sup> have shown that the character of the lesion produced in animals varies with the virulence of the micro-organism Very virulent strains of the bacillus of glanders rapidly cause necrosis of tissue and formation of small abscesses in the liver, lungs and other organs, whereas less virulent organisms produce nodules which are composed of epithelioid and giant cells and have all the characters of tubercles

The specificity of the tubercle is impaired by the observation that various sterile foreign bodies produce somewhat similar nodular lesions When, for example, finely powdered meal (Kopec<sup>29</sup>) in suspension is introduced into the peritoneal cavity, the particles are collected together in clumps and tubercle-like nodules are formed about the clumps scattered upon the peritoneal surface In other respects these foreign body tubercles do not accurately reproduce the histological peculiarities of the true tubercle Similar foreign body tubercles have been found scattered throughout the peritoneal cavity when, under conditions which cannot be accurately defined, food particles have entered the cavity through a perforation in the wall of the gastro-intestinal tract

It is well known that the tubercle bacillus contains an insoluble wax-like substance on which, in part at least, depends its ability to resist solution in the tissues, it is not improbable that its peculiar staining properties are dependent on the same substance Such wax may be obtained by extraction from tubercle bacilli and introduced in suspension into the body of an animal first attracts polynuclear leucocytes, later mononuclear phagocytes accumulate, and among them occur giant cells At the periphery a fibrous capsule is formed, the wax remains undissolved (Tschistowitsch<sup>30</sup>)

One form of pseudo-tubercle accurately reproduces the histological characters of the true tubercle About the eggs of the blood-fluke *Schistosoma japonicum* deposited in the liver and in the intestinal wall nodules with all the characters of true tubercles are formed Through the kindness of Dr Henry J Nichols,<sup>31</sup> I have lately had opportunity to examine tissues from a case of schistosomiasis occurring in the Philippine Islands The nodules are composed of epithelioid cells containing giant cells, at the periphery of the nodule lymphoid cells are abundant Coagu-

28 Duval and White Jour Exper Med, 1907, ix, 352

29 Kopec Beitr z path Anat u z allg Path (Ziegler's), 1904, xxxv, 562

30 Tschistowitsch Zeitr z path Anat u z allg Path (Ziegler's), 1907, xlvi, 163

31 Phalen and Nichols Philippine Jour Sc, 1907, iii, 223

lation necrosis with the histological characters of caseation occurs in the center of the nodules in contact with the egg, and the epithelioid cells at the margin of the necrotic area assume the arrangement frequently seen in true tubercles, namely, with long diameter at right angles to the margin of necrosis.

The observations just described suggest that the tubercle has a close relationship, on the one hand, to the late stage of acute inflammation at a time when absorption is in progress and, on the other hand, to the changes which occur about an insoluble substance. The histological data which are available, fail to furnish conclusive evidence concerning the origin of the macrophage, which has an important part in acute inflammation, nor of the epithelioid cell of the tubercle. Both cells are capable of ingesting and dissolving protein bodies, and both contain enzymes with similar properties.

The dog offers a favorable opportunity for study of the enzymes of tuberculous tissue and for comparison of these enzymes with those present in the sterile inflammatory exudates which are readily obtainable from the same animal.<sup>32</sup> When tubercle bacilli are injected into the pleural cavity, an immense mass of tuberculous tissue is formed in the mediastinum and the adjacent lymphatic glands undergo enormous hypertrophy. The power of this tissue to digest protein material exhibits certain noteworthy peculiarities. During the first two or three weeks after its formation polynuclear leucocytes are abundant and it exhibits the ability inherent in the leucoprotease of these cells to digest in the presence of an alkaline medium. At a later period with the disappearance of polynuclear leucocytes, this property diminishes and is finally lost. In the early period of its formation the tuberculous tissue digests in weak acid as well and at a later period when leucoprotease is no longer demonstrable the power of energetic digestion in acid persists. The enzyme which has this property may be extracted from the cells with water and preserved during a limited period of time. There is little doubt that it is contained in the epithelioid cells which digest within their substance tubercle bacilli, polynuclear leucocytes, red blood corpuscles and other cellular elements; for such cells constitute almost the entire bulk of the newly formed tuberculous tissue. Moreover, when the tuberculous tissue undergoes caseation and the epithelioid cells undergo necrosis so that a fibrous capsule alone persists, protein-digesting activity disappears from the tissue.

Autolysis in the presence of acid is exhibited by the liver, spleen and kidney, and these organs exert a limited power to digest foreign protein. There are at present no available means of determining if the enzyme of

<sup>32</sup> Opie and Barker Jour Exper Med., 1908, x, 645, 1909, xi, 686

tuberculous tissue is a peculiar enzyme or is identical with the autolytic enzyme of certain other tissues. Of especial interest is the observation that the enzyme of phagocytic cells which are capable of intracellular digestion is more active than the autolytic enzymes. Opportunity for an accurate comparison is afforded by the liver studded with innumerable miliary tubercles. Such tissue contains much more enzyme than normal liver.

A peculiarity of the serous effusion which accumulates in the infected pleural cavity in contact with the tuberculous tissue previously described emphasizes what has been said concerning the character of the enzymes contained in this tissue. Such serous effusion, like other serous effusions, inhibits the enzyme of the polynuclear leucocytes but unlike the serum of all other inflammatory exudates which have been tested, fails to restrain the enzyme which is abundant in the tuberculous tissue.

To complete the study of enzymes produced during the course of an inflammatory reaction, it is necessary to examine the adjacent lymphatic nodes. Such tuberculous nodes show enzymatic action which differs in no respect from that of the tuberculous mediastinum. The sinuses of the node are filled with large mononuclear phagocytes, many of which contain tubercle bacilli. Before caseation has begun, the histological appearance resembles that of the same node during the late stages of pleurisy produced by a sterile irritant such as aleuronat, and in both instances there is active enzymatic power of the same character.

Evidence of the existence of lipolytic enzyme in the cells of tuberculous exudates and in similar mononuclear cells from other sources has been obtained first by Bergel<sup>33</sup>. On plates of wax small excavations are produced after a period of incubation by exudates containing lymphocytes and especially by the exudate obtained from so-called tuberculous abscesses; ordinary pus produces no superficial solution of the wax plate. Tuberculous pus-like exudates, moreover, are capable of splitting neutral fat obtained from butter. Lymphatic gland and spleen pulp have similar lipolytic action, but bone-marrow, according to Fiessinger and Marie,<sup>34</sup> who have confirmed the observations just cited, fails to exhibit it. These authors have injected wax and various fats into the subcutaneous tissues and peritoneal cavity of animals and have found that polynuclear leucocytes first accumulate, an intense mononuclear reaction follows and effects the absorption of the fat. They think that the wax-like substance of the tubercle bacillus is dissolved by the lipolytic enzyme of the mononuclear cells.

33 Bergel Munchen med Wchnschr, 1909, lvi, 64

34 Fiessinger and Marie Arch d mal du coeur, 1909, 11, 545

The conditions under which in the body the intracellular enzymes act and the factors which bring them into action are not clearly understood. Intracellular digestion by amebas and other protozoa occurs in the presence of an acid medium and granules of litmus, and other indicators ingested by amebas undergo the usual color changes indicative of an acid reaction. When phagocytic cells of vertebrates are allowed to ingest such indicators in granular form, no such change of color occurs. Whatever change of reaction occurs is not indicated by this gross method.

The enzyme of the polynuclear leucocytes is active in a neutral or alkaline medium and its behavior *in vitro* indicates that the reaction of the normal body fluids is favorable to it. The acids, such as acetic acid, which have usually been employed to demonstrate the activity of the enzyme of the mononuclear phagocytes are not present in the cells or in the serum. Nevertheless, other acidifying substances such as carbon dioxide, or lactic acid, are capable of bringing the enzyme into action. It is not improbable that conditions which diminish the oxidation of pathological tissue or inhibit its gaseous interchange, increase its acid content and produce conditions favorable to the action of the enzyme.

Solution of bacteria, such as pyogenic cocci, is doubtless effected by the proteolytic enzymes contained within the polynuclear leucocytes. Metchnikoff has brought abundant proof that living bacteria are ingested by the leucocytes but it is uncertain what part enzymes have in destroying bacteria. The proteolytic enzyme of the leucocytes and the bactericidal complement of the serum are not identical. Abundant histological evidence previously cited has shown that the mononuclear cells which accumulate at the primary site of inflammation dissolve within their substance polynuclear leucocytes, many of which have probably undergone degenerative changes before they have been ingested, this process is continued and completed in the adjacent lymphatic nodes. Indeed, it is not improbable that polynuclear leucocytes, together with other products of tissue degeneration, serve as the principal stimulus to the activity of the mononuclear cells. Such intracellular digestion of polynuclear leucocytes is the first step in the resolution of an inflammatory exudate. There is scant evidence that polynuclear leucocytes disappear by autolysis unless suppuration occurs.

Absorption of fluid constitutes a second factor in the resolution of an exudate. When, with diminishing activity of the inflammatory irritant, exudation from the blood-vessels ceases, the physiological factors which favor absorption of tissue juices rapidly diminish the accumulated fluid unless the inflammatory irritant or inflammation itself has produced changes which alter the adjacent vascular and lymphatic structures,

necrosis, suppuration, which is always accompanied by necrosis, and new formation of fibrous tissue, three conditions which are usually associated, produce such structural changes.

The large mononuclear cells which act as phagocytes are at first only slightly larger than the cells which they ingest, but those which are engaged in digesting many cells attain great size. The fate of these large cells after they have accomplished their function is probably not always the same. Some may enter lymphatics and reach adjacent lymphatic nodes. According to Maximow, some undergo degenerative changes, whereas others remain in the tissue. It is not improbable that disappearance of exuded fluid produces conditions unfavorable to their prolonged existence and many probably undergo autolysis. Diminished blood-supply and other factors which might impair oxygenation doubtless increase the acidity of their protoplasm and favor self-digestion.

Human pathology affords numerous instances in which inflammation pursues its course without noteworthy destruction of tissue and, followed by complete restoration to normal, is unaccompanied by any fibrous induration of the part. Lobar pneumonia, acute serofibrinous pleurisy and erysipelas may be cited. Such inflammatory reactions are well represented by the serofibrinous inflammation which follows the introduction of turpentine into the pleural cavity of an animal. The fibrin of such an exudate undergoes autolysis *in vitro* under conditions which indicate the presence of leucoprotease only during the first three days after onset of the reaction. During this early stage autolysis occurs when the fibrin is suspended in weak acid and this ability to undergo self-digestion in acid persists at a later stage when fluid has completely disappeared from the chest. Fibrin obtained by whipping freshly drawn blood exhibits the same property. Since the blood-serum contains an enzyme exhibiting similar proteolytic activity it is probable that fibrin carries with it some of this enzyme when it is precipitated during coagulation. Autolysis referable to the presence of this enzyme may explain the disappearance of fibrin which persists after the fluid of an exudate has been absorbed. In some instances under conditions which are not understood, fibrin fails to undergo absorption and organization with new formation of fibrous tissue follows, fibrin is then slowly absorbed and replaced.

Further evidence that formation of scar tissue is not a necessary result of inflammation even when the reaction is inaugurated by extensive destruction is afforded by recent experiments of Whipple and Sperry<sup>35</sup> on the necrosis of the liver after poisoning by chloroform. The hepatic cells constituting a large part of the liver lobule undergo coagulation

necrosis, a considerable number of large mononuclear phagocytes collect at the site of injury and accomplish the absorption of the dead liver cells. By active multiplication of adjacent liver cells, the parenchyma which has been destroyed is replaced and no new formation of fibrous tissue follows. The liver is restored to normal and there is complete absence of cirrhosis, though a bit of tissue removed three weeks before has demonstrated necrosis of three-fifths of each hepatic lobule.

Human pathology affords little evidence that tuberculous exudates may undergo resolution with restoration to normal, yet such resolution is doubtless possible and is probably accomplished by the same enzymotic action, which brings about the disappearance of an acutely formed exudate. Experiments of J. L. Nichols<sup>36</sup> have shown that the exudate of tuberculous pneumonia in immune rabbits undergoes complete resolution.

After suppuration has occurred, restoration to normal by the processes which have been described is no longer possible. The inflammatory reaction pursues the course which brings it to an end only when enzymes set free by disintegration of polynuclear leucocytes are fully held in check by the serum which accumulates. When intensity of the irritant calls forth increasing numbers of leucocytes, and the density of the tissue affords restricted opportunity for accumulation of fluid, free enzyme overbalances antienzyme and fibrin, necrotic tissues, and perhaps to a limited extent adjacent living tissues undergo solution, in the wall of the abscess fibrous tissue is formed, what is the immediate stimulus to the new formation of fibrous tissue has not been determined.

Since long-continued inflammation is associated with new formation of fibrous tissue, such sclerosis has been commonly used as an index of chronic inflammation. Increase of interstitial tissue may furnish evidence of pre-existing inflammation even though the regenerative changes in the connective tissue are not included in the conception of inflammation. Nevertheless, the resulting confusion has introduced many inconsistencies into the nomenclature of disease.

In many instances of hepatic cirrhosis, the increased interstitial tissue is sclerotic and scar-like and all evidence of inflammation is wanting, the lesion, indeed, has all the characters of a scar and chronic hepatitis is not more applicable than is chronic inflammation to the scar from a burn of the skin (Marchand). The same remark is applicable to certain instances of granular atrophy of the kidney and to chronic lesions of other organs. Such diseases are a combination of degenerative change, notably necrosis, inflammatory reaction, regeneration of parenchymatous

elements and regenerative changes affecting the interstitial tissue. The relationship of these processes has not been sufficiently analyzed.

In most instances of so-called chronic endocarditis the existing lesion, perhaps preceded by inflammatory changes, is sclerosis of the valvular segments, and functional derangement of the valve is referable to peculiarities of scar tissue found in any part of the body. The same objection is applicable to fibrous myocarditis, applied to the lesion which occurs in association with arterial disease, impairing the vascular supply of the cardiac muscle. The common designation of chronic arterial disease does not have the affix "itis" indicating its inflammatory origin but arteriosclerosis is used almost synonymously with endarteritis and mesarteritis, lesions in which degenerative and regenerative changes are conspicuous, whereas true inflammatory reaction is in most instances wholly absent. Thoma has pointed to the truth that the present use of the term "chronic inflammation," applied to the liver, kidney, heart, blood-vessels and other organs, means nothing more than chronic disease. Study of pathological structure, eagerly pursued during the last two centuries, is not infrequently regarded as an unprofitable field for investigation and perhaps this view is correct should its scope be limited to the observation and description of pathological lesions, but examination of present knowledge concerning the nature and classification of various forms of inflammation shows how meager is our knowledge concerning the significance of altered structure.

If it were possible to define the origin of the mononuclear cells concerned in the inflammatory reaction of all vertebrate animals as well as it is possible to define the character and source of the common polynuclear leucocytes concerned in the same phenomenon, it might be possible to describe with an accurate generalization the essential nature of the cellular accumulation which follows the action of substances foreign to a tissue. The possibility that the various mononuclear cells which accumulate are derived from the lymphocytes of the blood, offers attractive solution of the matter, but proof is wanting. A definition of inflammation, as Metchnikoff has pointed out, must be applicable to the entire animal kingdom unless it can be shown that the changes which follow the same stimulus in one group of animals are different from those which occur in another group. Metchnikoff has shown very clearly that the possession of a well-formed vascular system does not furnish this distinction.

In order that the cells which accumulate at the site of inflammation may preserve their vitality, a proper medium is essential, exudation of serous fluid serves to dilute the inflammatory irritant and doubtless to furnish to migratory cells a suitable habitat.

To survive, an organism must prevent, or at least set a limit on, the entrance of foreign substance. Identical phenomena follow the entrance both of an insoluble foreign body and of a living invader capable of multiplication. The exclusion of inanimate material is relatively simple, but the struggle of one group of living beings to exclude other groups has been the source of almost infinitely complex relationships. The difficulty of distinguishing what is physiological and what pathological is here obvious. Since partial exclusion of bacteria is an essential condition of life, it is not inconceivable that special powers which accomplish no other physiological function may have developed. Phagocytosis of inanimate particles, such as carmine and charcoal, occurs equally well in serum and in normal salt solution, but most bacteria must be altered by the serum (acted on by opsonin) in order that phagocytosis attain its maximum activity. It is probable that agglutination and precipitation have a part in the phenomena which, during the course of an inflammatory reaction, fix and finally destroy certain inflammatory irritants. The bactericidal substances of the serum, both those which are normally present and those which are formed during the progress of immunization, are brought by exuded serum to the site of inflammation. Serum and cells cooperate.

From another point of view, cellular migration from the vessels and within the tissues may be regarded as a process by which certain enzymes are quickly concentrated at a point where they are needed. Study of the protein-digesting enzymes of inflammatory exudates has shown that cells and serum must maintain certain quantitative relations in order that the inflammatory reaction may accomplish its purpose and permit restoration to normal without excessive destruction and regeneration of tissue. Disturbance of this balance is followed by grave consequences which give to suppuration much of its ominous character.

Throughout the animal kingdom, the inflammatory reaction affords means by which various substances, notably enzymes, are delivered in unusual quantity in response to unusual local need. Inflammation may be defined as the process by means of which cells and serum accumulate about an injurious substance and tend to remove or destroy it. In lower animals with no vascular system this process with little or no accumulation of fluid occurs in the supporting tissues. In higher animals, it begins in the supporting tissues, proceeds with the cooperation of the blood-vessels and is completed in the adjacent part of the lymphatic system.

#### SUMMARY

Inflammation is a process which tends to render harmless an injurious substance, it has its site in the interstitial tissue of the body. This tissue consists of fixed cells and fibrillated substances and is penetrated by closed lymphatic vessels. With inflammation certain cells migrate through the

wall of the blood-vessels of the part and enter the spaces within the interstitial tissue. Some of these cells are destroyed, others penetrate the endothelial membrane which forms the lymphatic capillaries and hence are carried by way of lymphatic vessels to the regional lymphatic nodes.

Bacteria and many other injurious substances are attacked and ingested by the polynuclear leucocytes which migrate from the blood-vessels. These leucocytes, often injured by the inflammatory irritant, are in turn ingested by large mononuclear cells (macrophages) which quickly appear at the site of inflammation. The origin of these mononuclear cells is still undetermined. Ingestion of polynuclear leucocytes and other cellular material is begun at the site of inflammation and completed in the regional lymphatic nodes.

The ability of phagocytic cells to remove injurious material is dependent on the possession of proteolytic enzymes. Peculiar to the polynuclear leucocytes is an enzyme which, like trypsin, exerts its digestive action in an alkaline medium. The serum of the blood contains an antienzyme which restrains the action of this enzyme should it be set free by disintegration of the leucocytes, the action of the enzyme is thus limited to the locality in which it accomplishes its proper function, namely, within the cell. When enzyme is set free in such quantity that it overbalances the antienzyme of the exuded serum, suppuration occurs, for the purulent exudate has in virtue of its unrestrained enzyme acquired the power to soften and erode the adjacent tissues.

The mononuclear phagocytes which appear in the late stages of acute inflammation, the similar cells which appear in the regional lymph-nodes, and the cells of similar structure which constitute the greater part of tuberculous tissue contain an enzyme which, like pepsin, digests in the presence of acid. Such phagocytes are active at the site of inflammation but their work is completed in the regional lymphatic nodes.

Inflammation is the process by means of which cells and serum accumulate about an injurious substance and tend to remove or destroy it. This process does not include the regenerative changes which replace injured tissue by newly formed parenchymatous elements or by new interstitial tissue. Present nomenclature of chronic disease contains many terms which are inconsistent with knowledge of the underlying disease. Terms such as "parenchymatous nephritis," "traumatic myelitis," acute "hemorrhagic pancreatitis" are applied to conditions which have not primarily the characters of inflammation, the term "chronic inflammation" is applied to complex morbid changes (e.g. cirrhosis, chronic nephritis, myocarditis, arteriosclerosis, etc.) in which inflammatory processes have an insignificant part.

## A STUDY OF HEMOGLOBIN OF COLORED LABORERS IN PANAMA\*

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In a region like Panama, where blood-destroying diseases are so prevalent, the hemoglobin content of the blood and its variations are of special significance. The present work was undertaken in order to determine the relative effect on hemoglobin of certain conditions and infections. The results of the study will be discussed under the following heads:

I The approximate normal hemoglobin of the colored man of the tropics.

II The hemoglobin variation between natives of different West Indian islands furnishing the largest number of laborers for the work on the canal

III The relative frequency of infections

IV The influence of certain infections on hemoglobin

V The influence of climate, work and food on hemoglobin

The tables given were constructed from hemoglobin estimations, by a uniform method, in 359 consecutive patients from the ranks of the colored male laborers of the Isthmian Canal Commission. The estimations were made on the day following admission to the hospital, and the patients were usually within the first three days of their illness. The instruments used were two Sahli hemometers, one of which, after agitation of the standard tube, needed a 13 per cent reduction to standardize it to the other. The latter was found to be approximately correct by determining the color index in a number of normal persons. We found that it was necessary to modify Sahli's technic slightly in order to get uniform results with his instrument. Sahli introduces the blood immediately into tenth-normal hydrochloric acid and then dilutes with water. This technic gives readings which are too high and which may vary widely with blood from the same patient. But uniform readings may be obtained and the error greatly reduced if the blood is introduced first into a small quantity of water, and tenth-normal hydrochloric acid then added until the brown color of acid hematin is obtained. The necessary dilution with water is then made.

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\* Read at the meeting of the Canal Zone Medical Society, Jan 5, 1907

Examinations of blood for malarial parasites were made with dried films stained by Hasting's method. Microscopic examinations of stools for intestinal parasites or ova were made with fresh fluid or semifluid stools voided after a saline cathartic. The preparations were made by withdrawing small portions of the fluid stool from the bottom of the containing vessel with a pipette. The ova of parasites settle out quickly and are readily found by this method.

#### I NORMAL HEMOGLOBIN OF THE TROPICAL COLORED MAN

A series of forty-nine patients from Barbados, the most healthful of the West Indian islands, was studied in order to determine the approximate normal hemoglobin of the colored race of the tropics. These forty-nine patients were admitted to the hospital early in the course of uncomplicated malarial fever, they had had no former illness in Panama. Their average hemoglobin was 80.4 per cent. Since the patients entered the hospital very soon after the onset of their illness, it is probable that their hemoglobin had suffered but a slight reduction. We think, therefore, that a figure somewhat above 80.4 per cent, about 83 to 85 per cent, may be fairly considered normal for the healthy colored man of the tropics.

Emerson<sup>1</sup> reports hemoglobin estimations of the blood of students of the Johns Hopkins Medical School. These were normal men during the third decade of life, an age with which our series closely corresponds. He found that with uncorrected instruments the hemoglobin varied as follows: Gower hemoglobinometers, 150 students, 70 to 120 per cent, mean about 92 per cent; Fleischel hemoglobinometers, 176 students, mean 92.5 per cent; Dale hemoglobinometers, 156 students, mean 95 per cent.

#### II VARIATION WITH NATIONALITY

The patients were not numerous enough to enable us to make a comparative study of the hemoglobin of healthy men from all the West Indian islands represented. However, we compared the average hemoglobin of the patients from three islands furnishing the largest number of laborers. These patients were suffering from the same disease—malarial fever uncomplicated or associated with uncinariasis, amebiasis, etc.

197 Barbadians	Average hemoglobin 72.7 per cent
19 Jamaicans	Average hemoglobin 73.7 per cent
18 Martiniquans	Average hemoglobin 55.2 per cent

The Martiniquans, therefore, were fair inferior in hemoglobin to the Barbadians and Jamaicans, who were practically equal.

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<sup>1</sup> Emerson Clinical Diagnosis, p. 365

## III RELATIVE FREQUENCY OF INFECTIONS

*Malarial Fever*—There were 277 patients from Barbados, Jamaica and Martinique. Of these, 234, or 84.5 per cent, were admitted to the hospital on account of malarial fever. In about 80 per cent of the malarial patients, parasites were demonstrated in the peripheral blood, and of these about three-fourths were infected with estivo-autumnal organisms. There were five quartan infections, and the remainder had tertian parasites.

*Uncinariasis*—Of the above 277 patients 36.1 per cent had uncinariasis. Of the Barbadians 34 per cent were infected, Jamaicans, 53.6 per cent, Martiniquans, 66.6 per cent. This percentage applies not only to hospital patients, but to all colored laborers from these islands, for the patients were not admitted on account of uncinariasis, but the infections were found incidentally during routine examinations of stools.

*Amebiasis*—Intestinal amebiasis was found in eighty-eight, or 24.5 per cent, of 359 patients, in sixty instances *Entamoeba histolytica* was present, in twenty-eight, *Entamoeba coli*.<sup>2</sup> Among the eighty-eight patients there were seven with dysentery—8 per cent. All the dysentery patients were infected with *Entamoeba histolytica*, and two of them had abscess of the liver.

*Other Diseases*—Small groups of the following diseases aggregated about 15 per cent of the total number of patients: pneumonia, typhoid fever, dysentery (acute unclassified), tuberculosis, nephritis, etc.

## IV INFLUENCE OF INFECTIONS ON HEMOGLOBIN

The only infections presenting groups sufficiently large to be of consequence were malarial fever, uncinariasis and amebiasis. To study the effect of these infections it was necessary to have a large group of patients who had lived approximately under the same conditions. The Barbadians, therefore, were chosen as furnishing the best material on which to base the study. Among 197 Barbadians, 130 had uncomplicated malarial fever—excepting amebiasis without dysentery and other less important intestinal infections, such as trichocephaliasis, strongyloidosis, etc., sixty-seven had combined malarial and uncinarial infections. There were a few intestinal infections, each with *Bilharzia* and *Balantidium coli*. The tables indicate the effect on hemoglobin of previous attacks of malarial fever when uncomplicated and when complicated with uncinariasis and amebiasis.

<sup>2</sup> Late study of amebas by staining leads us to doubt whether or not we can safely differentiate the species in the flesh specimen.

*Malarial Fever*—In Table 1 there is a decided tendency for the hemoglobin percentage to decrease as the number of previous attacks of malarial fever increases, also the relative number of cases of anemia (arbitrary standard, hemoglobin 60 per cent or less) increases with more numerous previous attacks. This is true until one reaches the group of patients in Table 1, who have had six or more previous febrile attacks. In this group there is a relative diminution of the number of cases of anemia, and one is surprised to find that there is an increase of 7 per cent of hemoglobin over the group of patients that have had 3 to 5 previous attacks. This phenomenon suggests relative immunity or tolerance for the malarial poison.

TABLE 1—MALARIAL FEVER

No of Previous Febrile Attacks	No Cases	No Cases of Anemia, Hb 60 Per Cent or Less	Average Hb Per Cent
0	49	1	80.4
1 or 2	39	5	75
3-5	23	7	65
6 or +	19	2	72
Total	130	15	75

TABLE 2—MALARIAL FEVER AND UNCINARIASIS

No of Previous Febrile Attacks	No Cases	No Cases of Anemia, Hb 60 Per Cent or Less	Average Hb Per Cent
0	18	1	75
1 or 2	24	9	67.5
3-5	14	4	70
6 or +	11	4	62
Total	67	18	69

TABLE 3—MALARIAL FEVER AND AMEBIASIS

No of Previous Febrile Attacks	No Cases	Average Hb Per Cent
0	11	79
1 or 2	7	74.1
3-5	2	57
6 or +	5	65
Total	25	73

TABLE 4—MALARIAL FEVER, UNCINARIASIS AND AMEBIASIS

No of Previous Febrile Attacks	No Cases	Average Hb Per Cent
0	4	81
1 or 2	4	69
3-5	3	70
6 or +	3	73
Total	14	73.3

*Uncinariasis*—Table 2 when compared with Table 1 shows that uncinariasis causes a well-marked diminution of hemoglobin in the colored race, the average being 6 per cent less than in uncomplicated malarial fever. Moreover, the number of patients with anemia (hemoglobin 60 per cent or less) is more than doubled when malaria is complicated with uncinariasis, the proportion of anemias with combined

infections being 1 in 37, against 1 in 87 in uncomplicated malarial fever. Uncinariasis also appears to prevent a rise of hemoglobin in the group of patients who have had six or more previous febrile attacks, and who, according to Table 1, should have established a tolerance for the malarial poison.

When it is considered that none of the patients entered the hospital on account of uncinariasis, that the infection was discovered incidentally in routine examinations, and that the proportion of these patients infected represents approximately the proportion of colored laborers infected throughout the Canal Zone, one sees what an enormous amount of blood destruction in the aggregate must be caused by uncinariasis, and how numerous must be the cases of weakness and anemia due to it.

*Amebiasis*—Tables 3 and 4 compared with Tables 1 and 2, respectively, show that amebiasis without dysentery does not play an important rôle in blood destruction. The infection with dysentery occurred in such a small number of cases that the anemia due to it was relatively unimportant.

*Jamaicans and Martiniquans*—The groups from the islands of Jamaica and Martinique were relatively small, but as far as they go they confirm the results obtained by a study of the Barbadians. Among nine Jamaicans with uncomplicated malarial fever, none were anemic, among ten with malaria and uncinariasis two were anemic. Among four Martiniquans with malaria two were anemic, among fourteen with both infections nine were anemic (hemoglobin 60 per cent or less), i.e., 66.6 per cent were infected with uncinaria, and 61 per cent were anemic.

#### V EFFECT OF CLIMATE, WORK AND FOOD ON HEMOGLOBIN<sup>3</sup>

In studying this subject, we considered that the effect of time spent on the Isthmus of Panama might be taken as an equivalent of the effect of climate, work and food. Barbadians with uncomplicated malarial fever were used, and 130 cases divided into groups according to the number of months spent in Panama.

TABLE 5—UNCOMPLICATED MALARIAL FEVER IN BARBADIANS, HEMOGLOBIN PER CENT ACCORDING TO TIME IN PANAMA

Months in Panama	No Cases	Hb Cent or Less	60 Per Cent	Average Hb
Less than three	49	4	77	
Three to five	33	4	74.5	
Six to nine	34	7	70	
Ten or more	14	0	76.5	
Total	130	15	75	

<sup>3</sup> This work was done in 1906, before the laborers were fed by the Isthmian Canal Commission.

If the average hemoglobin of these groups is compared with that in Table 1, it will be seen that variations according to the number of months spent on the isthmus are exactly similar to variations due to previous attacks of fever, but are not nearly so marked, i.e., the variations bear a closer relation to previous febrile attacks. It is probable, therefore that the variations in Table 5 were due to the fact that the number of attacks of fever increase directly with the time spent on the isthmus, as shown in Table 6.

TABLE 6—BARBADIANS, JAMAICANS AND MARTINIQUEANS,  
NUMBER OF ATTACKS OF FEVER, ACCORDING TO  
TIME IN PANAMA

Months on Isthmus	BARBADIANS		
	No Patients	Total Febrile Attacks	Average No Attacks Per Patient
Less than three	82	48	0.6
Three to five	60	95	1.6
Six to nine	43	160	3.7
Ten or more	40	171	4.3
JAMAICANS			
Less than three	1	0	
Three to five	10	14	1.4
Six to nine	3	8	2.7
Ten or more	12	45	3.9
MARTINIQUEANS			
Less than three	0		
Three to five	0		
Six to nine	21	64	3
Ten or more	5	32	6.4

In each group the number of attacks of fever vary directly with the number of months spent on the isthmus. The Jamaicans have been on the isthmus longer than the Barbadians, yet their average hemoglobin is slightly higher than that of the latter, and this in spite of the fact that the former are more largely infected with *uncinaria*. This seems to be due to the fact that the Jamaicans have had fewer attacks of fever, with longer intervals between the attacks.

In order to eliminate as far as possible the influence of infections however, we have taken each group of Table 1 (the groups representing so many previous attacks of fever) and subdivided it into groups representing time spent on the isthmus. Subgroups containing less than 3 cases are omitted in Table 7.

The subgroups show very slight differences within the same main group, and these differences bear no relation to the number of months spent on the isthmus. The main groups, however, show well by this arrangement a definite relation between the hemoglobin decrease and an increased number of previous attacks of fever. Attention is called again

to the unexpected rise of hemoglobin in the group of patients who have had six or more previous febrile attacks, suggesting relative immunity or increased tolerance for the malarial poison.

TABLE 7—BARBADIANS WITH MALARIAL FEVER, HEMOGLOBIN ACCORDING TO NUMBER OF ATTACKS AND TIME ON Isthmus

Months on Isthmus	FIRST FEBRILE ATTACK		
	No of Patients	Hb Cent or Less	Average Hb Per Cent
Less than three	34	1	80
Three to five	13	0	81
Six to nine			
Ten or more			
ONE OR TWO PREVIOUS ATTACKS			
Less than three	12	2	74.5
Three to five	15	2	71
Six to nine	8	1	75
Ten or more	4	0	81
THREE TO FIVE PREVIOUS ATTACKS			
Less than three	3	1	67
Three to five	3	1	66
Six to nine	15	5	62
Ten or more			
SIX OR MORE PREVIOUS ATTACKS			
Less than three			
Three to five			
Six to nine	10	1	80
Ten or more	7	0	77

From a study of these tables we think that it is fair to conclude that conditions of life on the isthmus—that is, climate, work and food—in themselves have no detrimental effect on the hemoglobin content of the blood of colored laborers, and that the loss of hemoglobin is a question of infections, and of infections only. We feel safe in saying, also, that this is true for white Americans on the isthmus, though our observations have not yet been analyzed.

#### SUMMARY

- 1 The average hemoglobin of healthy colored men of the tropics is about 83 to 85 per cent.
- 2 The average hemoglobin of Barbadian and Jamaican laborers was 72.7 and 73.7 per cent, respectively, that of Martiniquans 55.2 per cent.
- 3 Of 277 patients, 234, or 84.5 per cent, had malarial fever, 15.5 per cent had pneumonia, typhoid, dysentery, liver abscess, tuberculosis, nephritis, etc. Uncinariasis was found in 36.1 per cent, amebiasis in 24.5 per cent.
- 4 The hemoglobin curve of malarial patients varies inversely with the number of previous attacks of malarial fever until a relative immunity or tolerance for the malarial poison is developed, when a rise of hemoglobin occurs. This rise does not take place in patients infected with uncinaria.

Uncinariasis complicating malaria in colored men causes a reduction of hemoglobin, which averages 6 per cent less than that of uncomplicated malarial infections. The complication causes more than double the proportion of anemic cases. Amebiasis without dysentery does not appreciably affect the hemoglobin curve.

5 Conditions of life on the Isthmus of Panama do not in themselves affect the hemoglobin of colored laborers. Blood destruction is a question of infection only.

We wish to thank Col W C Gorgas, Chief Sanitary Officer, for his permission to publish this report.

## PAROXYSMAL HEMOGLOBINURIA

AN EXPERIMENTAL STUDY OF A CASE

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In the case presented in this article, on which our work was performed, any severe chilling of the patient's skin caused a temporary hemoglobinuria, drowsiness, regurgitation of food and other minor symptoms to be mentioned later. The phenomena were produced either by a chilling of the general body surface or, what was more common, by the mere exposure of the hands and face to cold, damp winds, or by the wetting of the feet in cold weather. The phenomena were produced experimentally in the laboratory by dipping the patient's feet in water reduced to a temperature of 9 to 12 C, even when the general room temperature was 27 C.

Donat and Landsteiner<sup>1</sup> in 1904 based their explanation of paroxysmal hemoglobinuria on Ehrlich's side-chain theory. Eason,<sup>2</sup> in his admirable paper on this disease in 1906, explained the phenomena in the same way. Hoover and Stone<sup>3</sup> also have shown that the hemolysis preceding the hemoglobinuria may be explained by the side-chain theory. The amboceptor becomes attached to the red blood cells on exposure of the blood to a temperature of 5 to 15 C for fifteen minutes to one hour. The complement then causes hemolysis when the temperature of the blood is subsequently raised to body temperature for a few minutes. This experiment may be performed in a test-tube by using defibrinated blood.

Hoover and Stone have shown that, in the above experiment, the hemolysis may be prevented by the addition of cholesterol to the defibrinated blood. They have explained this by supposing that the amoceptors attach themselves to the free cholesterol instead of to the red cells. They have supposed that it is the cholesterol of the red cells to which the

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\* From the Physiological Laboratories of St Louis and Purdue Universities

1 Donat and Landsteiner Munchen med Wochenschr, 1904, 11, 1590

2 Eason Jour Path and Bacteriol, 1906, 11, 167

3 Hoover, C F, and Stone, C W Paroxysmal Hemoglobinuria, Account of Two Cases, THE ARCHIVES INT MED 1908, 11, 392

amboceptors attach in causing hemolysis Lecithin had no inhibitory effect when used in place of the cholesterol

Hoover and Stone administered cholesterol to their patients by mouth but were unable to state definitely that any benefit was produced, because their patients would not submit to further experimentation. Their patients had no subsequent attacks of hemoglobinuria but as the weather was moderate during this time no hemoglobinuria would be expected and the patients would not allow its production by means of an iced foot-bath.

Hoover and Stone were able to show, however, that calcium lactate would not inhibit the hemolysis produced by exposure to cold. This result was obtained whether the salt was given by the mouth, in doses of 60 grains daily, or was added to the blood in a test-tube.

Manwaring<sup>4</sup> has shown that calcium chloride, as well as other salts, inhibits the hemolysis of dog's corpuscles by goat's serum after the goat has been immunized against the dog's corpuscles.

As will be shown later, we have found in our patient that calcium chloride behaves somewhat like cholesterol in that it inhibits this hemolysis in the test-tube. Like Hoover and Stone we are unable to give definite conclusions after administration of the salt by the mouth because of the refusal of the patient to be experimented on further.

#### HISTORY OF CASE

*Patient*—F. N. S., aged 28, born in Rochester, N. Y., of German parentage, lived there twenty years, two years in Ohio, three years in Texas, and three years in St. Louis. He has always been in railroad work, is a switchman now. He has been married two years, has no children. His father died at 55 of dropsy of the heart, his mother is alive at 68 in good health. He has five brothers all in good health. One sister had "red urine" fifteen years ago, she had an operation (supposedly for the "red urine") and now enjoys good health. Two other sisters have always enjoyed good health. Our patient had "typhoid-pneumonia" in Rochester, no sickness in Ohio. He had typhoid in Texas in 1904. He lived in St. Louis a year before he had an attack of hemoglobinuria. He has had four attacks of gonorrhœa, the last one in 1905. He had warts on the penis in 1904—probably chancroids. The patient eats regularly, his appetite is good. He sleeps well, smokes much, does not drink alcoholic beverages. He has never had an attack of hemoglobinuria in the summer.

*Present Illness*—The first attack occurred in the fall of 1907 and consisted of one red urination after a chilling of the skin. Recurrences then followed every two or three weeks during the winter of 1907-08 or oftener, depending on the weather. An attack usually began with a chilly sensation (Hoover and Stone observed a subnormal temperature at the beginning of an attack, and we obtained it once experimentally). This chilling was followed by more or less vomiting, probably a simple regurgitation of food such as we noticed in our experiments. There was no accompanying nausea or pain. Dark red urine was passed for five to twelve hours afterward. There was much drowsiness, slight pain in the joints.

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<sup>4</sup> Manwaring, Jou. Infect. Dis., 1904, 1, 122.

on movement, particularly of the ankles. The skin of the face, hands or feet (that part exposed to the most cold) first showed a blanching, followed by edema and finally by hyperemia, with a return to normal in ten to twelve hours. A good night's rest in bed was sufficient to cause the patient to feel perfectly well except, possibly, for a slight drowsiness the following day.

*Examination*.—In November, 1908, the patient came under the care of one of us (Neilson) in St. Mary's Hospital, in St. Louis. A thorough physical examination at this time proved practically negative. The blood was examined as to the number of red and white cells, which were normal. No parasites were found. Examinations of the stomach and feces proved negative. Repeated examinations of the urine showed an intermittent albuminuria. The time of the occurrence of albumin was independent of the presence of hemoglobin. Sometimes the two substances occurred together. The experimental application of three small pieces of ice at points about one and one half inches apart on the back of the hand caused three local areas of edema, which became confluent, then hyperemic and finally disappeared in six to eight hours. This slight chilling did not cause hemoglobinuria (at least not to a degree appreciable to the eye).

At this time heavy woolen underclothing, felt boots and general instructions to keep warm were given the patient. Ten grains of calcium chloride three times daily were prescribed. The patient worked all of the winter of 1908-09 with only two very mild attacks of hemoglobinuria. One of these occurred after the patient had temporarily stopped taking the calcium chloride for a week. The calcium chloride caused no gastric disturbances.

#### EXPERIMENTS

In July, 1909, the following experiments were performed, the patient continuing to work as switchman for ten to fourteen hours daily. Because of this, and his reluctance to be experimented on, our results are not as complete as we could desire.

*General Methods*.—In determining the hemolytic power of the patient's serum, 10 c.c. of blood were drawn from the median basilic vein and were allowed to clot in a sterile centrifuge tube. The blood was later centrifuged and the serum constitutes the "h.s." (hemolytic serum) of the experiments. A 20 per cent suspension of washed blood corpuscles was obtained by allowing 1 c.c. of blood from the finger of the patient to run into a few drops of sterile 1 per cent potassium oxalate solution. The corpuscles were then washed eight times with sterile eighth-molecular sodium chloride solution by the aid of the centrifuge. The suspension was then diluted with sterile eighth-molecular sodium chloride to make a 20 per cent suspension of corpuscles. The calcium chloride and all glassware used in these experiments were carefully sterilized. In the experiments of July 28, it will be noticed that washed corpuscles were obtained from two sources, one was the patient himself the other was another man. In the experiments of July 16, only the latter were used. It will be noticed that in the experiments of July 28 slightly different results were obtained with the two different suspensions of corpuscles.

In the experiments of July 19 and 28, the hemoglobinuria was produced experimentally by immersing the patient's feet in water kept at 9 to 12 C by means of ice. The ice water was constantly thrown up over the patient's ankles. On July 19, this iced foot bath was continued for twenty minutes, on the 28th for thirty minutes. On both days the temperature of the room was about 27 C.

*July 16, 1909—I Experiments Determining the Inhibitory Effect of Calcium Chloride on the Hemolysis of Red Blood Corpuscles by the Patient's Serum—No*

calcium chlorid had been given internally to the patient for six months. Ten cubic centimeters of blood were drawn from the patient at 8 a m. This was allowed to clot for two hours, was then centrifuged. The serum obtained constitutes the "h s" of the experiments. One cubic centimeter of blood was drawn from another person at 8 30 a m. The corpuscles were washed eight times with sterile salt solution and were then diluted to 20 per cent of their original volume. These constitute the "b c" of the experiments.

The mixtures shown in Table I were made in small test-tubes (3 cc) at 11 a m.

TABLE I—HEMOLYTIC POWER OF PATIENT'S SERUM BEFORE TAKING CALCIUM CHLORID

1 1 cc m/8 NaCl + 0 2 cc hs + 0 5 cc 20 per cent b c	Placed immediately at 37 C. There was no laking until 4 30 p m and then it was slight
2 1 cc m/8 NaCl + 0 2 cc hs + 0 5 cc 20 per cent b c	Placed immediately at 3 C for 30 min, then at 37 C. After 20 min, at 37 C there was slight hemolysis. At 1 p m there was complete hemolysis
3 0 3 cc m/8 NaCl + 0 2 cc hs + 0 5 cc 20 per cent b c + 0 7 cc CaCl <sub>2</sub>	Placed at 37 C (as No 1). There was slight hemolysis at 3 p m (possibly of bacterial origin)
4 0 3 cc m/8 NaCl + 0 2 cc hs + 0 5 cc 20 per cent b c + 0 7 cc CaCl <sub>2</sub>	Placed at 3 C for 30 min, then at 37 C (as No 2). There was slight hemolysis at 3 30 p m

At 4 30 p m tubes 1, 3 and 4 looked alike, there was slight hemolysis in all. In tube 2 there was complete hemolysis.

This experiment was performed a second time. At both trials varying amounts of hemolytic serum and of calcium chlorid were used, but without changing the results.

The first point to be noted in this experiment is that, in Mixtures 1 and 3, which were not subjected to the low temperature of 3 C, but which were placed immediately at 37 C, there was only slight hemolysis, and this occurred only after four hours. This may have been due in part to bacterial action, what is more probable, however, is that there was sufficient cooling of the blood from 8 a m to 11 a m to cause some hemolysis to occur after the blood was placed at 37 C. From the time the blood was drawn (8 a m) to the time the mixtures were made (11 a m) the patient's serum was at room temperature, which was 27 C to 28 C. It was impossible to keep the blood at body temperature all of this time.

The second point to note is that hemolysis did occur readily in Tube 2. This tube was subjected to a temperature of 3 C for thirty minutes before it was placed at 37 C. Theoretically it was during the exposure to 3 C that the amboceptors became united to the red cells, the complements causing the laking when the blood was raised to 37 C for a few minutes.

The third point to note is that in Tube 4, the hemolysis was inhibited by the presence of 0 7 cc of m/8 CaCl<sub>2</sub> (in place of so much NaCl), although this tube was subjected to the same cooling and subsequent warming as was Tube 2 (in which there was complete laking).

July 19, 1909—II Experiments Determining the Effect of the Iced Foot bath (Applied for Twenty Minutes) on the Patient. No calcium chlorid had been given internally to the patient for six months.

TABLE 2—BLOOD COUNT AFTER ICED FOOT-BATH—NO CALCIUM CHLORID

Time	Body temp	Urine	Red Absolute	Blood Corpuscles				White			Relative (%)	L
				Absolute	Poly	LL	SL	M	Eos	Mono		
8 30 a m	98.4	Normal	5,200,000	11,520	62	23	12	2	3	0		
8 40 to 9 a m		Iced foot bath		Regurgitation of food at the end of time								
9 00 a m	97.8	Dark	5,680,000	10,100	62	23	8	1	3	3		
11 10 a m	98.7	Black	5,760,000	10,600	90	6	4	0	0	0		
2 30 p m	98.0	Brown	5,120,000	8,600	80	19	1	0	1	0		

The first point to which we wish to call attention is the apparent health of patient at 8 30 a m

The second point is the regurgitation of food at the end of the iced foot-bath, the subnormal temperature, the hemoglobinuria and the very slight change in the absolute number of red and white blood corpuscles. We have no explanation to offer for the changes in percentage of the white corpuscles. Careful differential counts were made by two different people—their results tallying—on different smears.

The third point is the other symptoms, the ankles first became edematous then hyperemic, returning to normal in about three hours. The patient became drowsy. The hemoglobinuria lasted for six hours. Patient felt as well as ever the following day.

*July 28, 1909—III Experiments Determining the Effect of the Internal Administration of Calcium Chlorid for Eight Days*—Immediately after the experiments of July 19, the patient was given ten grain doses of calcium chlorid three times a day for eight days. These experiments are divided into two parts.

1 At 8 a m 10 cc of blood were drawn from the median basilic vein. This blood was allowed to clot, the serum being used to determine the effect of the calcium chlorid on the hemolytic power in the test-tube. These experiments were similar to those performed on July 16 (before any calcium chlorid had been given to the patient). In these experiments we attempted to find whether there had been sufficient absorption of the salt into the blood to cause inhibition of the hemolysis.

2 At 8 37 a m the patient was given an iced foot-bath similar to the one of July 19, except that in this case the bath was continued for thirty minutes instead of twenty minutes, because at the end of twenty minutes the patient showed no signs of an attack of hemoglobinuria and said he was not going to have an attack. As is shown below, we did cause a mild attack by prolonging the bath.

1 Results of the experiments determining the hemolytic power of the patient's serum in the test-tube. These experiments were performed exactly as were those on July 16. In these, however, two different samples of corpuscles were used. Mixtures 1, 2 and 3 were made using the patient's own red blood cells, mixtures 4, 5 and 6 were made with corpuscles from the subject used for this purpose on the 16th. The blood was drawn at 8 a m. The mixtures were made at 11 30 a m.

TABLE 3—HEMOLYTIC POWER OF PATIENT'S SERUM AFTER TAKING CALCIUM CHLORID

1 0 5 cc m/8 NaCl + 0 4 cc hs + 0 25 cc bc	Placed immediately at 37 C No hemolysis at 5 p m
2 0 5 cc m/8 NaCl + 0 4 cc hs + 0 25 cc bc	Placed at 3 C for one hour, then at 37 C Slightly laked at 1 30 p m No more at 5 p m
3 0 5 cc m/8 CaCl <sub>2</sub> + 0 4 cc hs + 0 25 cc bc	Placed at 3 C for one hour, then at 37 C No hemolysis at 5 p m
4 0 5 cc m/8 NaCl + 0 4 cc hs + 0 25 cc bc	Placed immediately at 37 C No hemolysis at 5 p m
5 0 5 cc m/8 NaCl + 0 4 cc hs + 0 25 cc bc	Placed at 3 C for one hour, then at 37 C Complete hemolysis at 1 30 p m
6 0 5 cc m/8 CaCl <sub>2</sub> + 0 4 cc hs + 0 25 cc bc	Placed at 3 C for one hour, then at 37 C No hemolysis at 5 p m

The first point to be noted in this experiment is that not a sufficient amount of the calcium chlorid had been absorbed into the blood to inhibit completely the hemolysis in either tube 2 or 5.

The second is that there was more hemolysis with the foreign corpuscles (5) than when the patient's own corpuscles were used (2). These results were obtained when the blood serum was cooled to 3 C for one hour.

The third point is that the hemolysis produced by the exposure to the temperature of the 3 C was completely inhibited in Tubes 3 and 6 to which calcium chlorid was added in place of the sodium chlorid.

Fourth, another obvious point is that the hemolysis did not occur in those tubes (1 and 4) which were not subjected to the cooling (3 C), but which were placed immediately at 37 C.

2 Results of giving the patient an iced foot bath, the principal symptoms are briefly summarized in Table 4

TABLE 4—BLOOD COUNT AFTER ICED FOOT BATH, FOLLOWING CALCIUM CHLORID

Time	Body temp	Urine	White Blood Cells, Relative (%)					
			Poly	L L	S L	Mast	Eos	L Mono
8 30 a m	98.8	Normal			(Lost)			
8 37 to 9 07	Iced foot bath	No regurgitation of food						
9 10 a m	98.6	Brownish	68	26	4	0.5	0.5	1
10 10 a m	98.6	Normal	25	65	5	1	1	0
3 30 p m	98.6	Normal	77	17	0	2	2	2

The points to which we wish to call attention are, first the apparent health of the patient at 8 30 a m, second, the longer time during which the foot bath was given over that of July 19, and, third, the fact that the ankles did not show the edema that they did on July 19. There was no regurgitation of food, no subnormal temperature, and only slight hemoglobinuria for one urination. We have no explanation for the variations in the percentage of the white blood cells. The patient did not become drowsy. He said, after the bath that he felt as well as he ever did.

A long course of the internal administration of calcium chlorid was then attempted, but furunculosis occurred and the salt was discontinued after two months. No hemoglobinuria occurred during this time, the weather was not severe, however, and the patient refused to be further experimented on.

We cannot state definitely that calcium chlorid when administered by the mouth does prevent this hemoglobinuria, but in view of the inhibitory effect on hemolysis in the test-tube, and the apparent greater difficulty of producing hemoglobinuria by foot-baths after the administration of calcium chlorid, we feel justified in concluding that if sufficient calcium chlorid could be introduced into the blood, and retained, no hemoglobinuria would occur.

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ADAMS-STOKES' SYNDROME, WITH COMPLETE HEART-BLOCK, WITHOUT DESTRUCTION OF THE BUNDLE  
OF HIS

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That destruction of the auriculo-ventricular bundle of His in the mammalian heart will always cause heart-block has been repeatedly proved both experimentally and by numerous clinico-pathological observations within the last five years<sup>1</sup>. The converse of this proposition, however, that heart-block is always caused by destruction of the aforesaid bundle, has by no means been proved, and, in fact, it is most probable that there are several other causes that may produce this dissociation of auricular and ventricular rhythm. What these causes may be it is not yet possible to say, this paper is merely to show that complete heart-block and the symptoms of Adams-Stokes' syndrome may exist, not only without destruction of the bundle of His, but with insignificant lesions no greater than those found in normal bundles. Furthermore, following the principles established by the experiments of Erlanger and Hering, it has generally been supposed that partial heart-block was caused by partial destruction of the bundle of His (round-cell and fatty infiltration, partial sclerosis and so on), whereas complete block was supposed always to be caused by complete obstruction, but this is also contradicted by the pathological findings in the present case.

The patient, who presented the above conditions for at least more than five years, was under the care of Dr Robert Pittfield, to whom I am obliged for the pathological material and the clinical notes of the case. An abstract of the history is as follows<sup>2</sup>:

*Patient*—Captain D, 76 years old, widower former sea captain and dentist. Excellent family history. Always smoked considerable tobacco, never drank to excess, denies any syphilitic infection. In earlier life had a severe attack of acute articular rheumatism and also pneumonia. His present illness began seven

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From the Aye Clinical Laboratory of the Pennsylvania Hospital

<sup>1</sup> For bibliographies of heart-block and Adams Stokes' syndrome see van den Heuvel De Ziekte van Stokes-Adams, Doctorat Thesis, Groningen December, 1908, Pletnew Engeb d inn Med u Kinderheilk 1908, 1 47 and Univ Penn Med Bull, November, 1908 xxii 278

<sup>2</sup> For full report of the earlier history of the case see Pittfield Medicine Detroit, 1904, v, 654

years ago shortly after an attack of influenza and a long period of trying watching by the bedside of his wife, and he has been more or less invalided by it ever since. He easily becomes short of breath on exertion, such as climbing stairs, and feels his heart throbbing in his chest. His ankles occasionally become swollen so that his shoes feel tight, and there is also some gastric disturbance, as manifested by heartburn and gaseous eructations. If he undergoes any sudden exertion or sometimes even if straining at stool, he is subject to epileptiform attacks. These always give some warning and occur in the following manner. The pulse becomes slower and slower and when it reaches about 18 beats to the minute stops altogether for some seconds. The respiration becomes noisy and then stertorous. He feels that he is going off. The muscles of the face begin to twitch. The vessels of the neck become turgid and the face cyanotic, and consciousness is entirely lost. After a minute or two, the convulsion ceases, the pulse is manifest at the wrist, the eyes open, consciousness is restored and the patient is none the worse for the attack.

*Examination*.—In 1904 the patient was a hardy, weather-beaten man, with a marked aicus senilis and rigid temporal and radial arteries. Heart was hypertrophied, apex-beat in eighth space beyond the midclavicular line. There was a marked retraction of the chest wall after each ventricular systole. A blowing systolic murmur was heard at the apex. Pulse-rate 21, varied from 41 to 19. When the cardiosphygmograph was taken the ventricular rate varied from 28 to 30 per minute, the auricular rate from 60 to 70 and the auricular beats were shown to come quite independently of the ventricular. A drink of whisky temporarily raised the ventricular rate to 34. Synchronous with the pulse on auscultation, there was a heavy systolic contraction at the wrist, followed by two, three or rarely four minor, hurried aborted systolic sounds, that gave no palpable impulse at the wrist. The urine was slightly increased in amount, good color, normal specific gravity, no albumin or sugar. A few hyaline casts were constantly found.

*Course of Disease*.—The condition of the patient continued with but little change, except that the epileptiform seizures became more frequent and severe. Shortly before his death he had a particularly severe attack while sitting on a pot after taking magnesia, and his pulse rate went down to four beats to the minute. At this time his pulse rate was usually about 20 to 25, the auricular contractions plainly audible and the venous pulsation with the extra-auricular systoles plainly visible. It was noted that his general condition always tended to be worse, the slower his pulse rate was. One month before his death he began to suffer with intermittent claudication of the left leg. Almost every day he would have an attack of severe pain in the left leg, with pulse less marked on that side. This caused him to limp and often to fall down. For the last two weeks before his death, he was confined to his bed, did not recognize his friends, was rather flighty, but with no actual delusions. He became very weak and died suddenly late at night, without any premonitory signs—gave one gasp and fell over dead.

*Partial Autopsy*.—This showed cardiac hypertrophy, chronic interstitial nephritis (small red granular kidneys), chronic passive congestion of lungs and liver, marked arteriosclerosis.

*Gross Description of Heart*. (Heart has been preserved complete with the aorta in formalin.) The heart is quite large, weighing 490 gm. The epicardium is diffusely thickened and contains a moderate amount of fat. The right side, which has not been opened, still contains a good deal of post-mortem clot. The tricuspid and pulmonary valves appear quite thin and delicate. The left auricle is fairly large and capacious. There is perhaps some trifling thickening at the margins of the mitral valves and at the bases of the mitral valves there are thin,

opaque yellow plaques which are thicker than the valve substance. These extend beneath the posterior leaflet of the aortic valve, where perhaps they are densest, and one plaque extends for 0.5 cm over the septum ventriculorum. The septum itself is quite large, except for the little plaque very thin and delicate. About 3 mm below this small plaque the wall of the ventricle begins. One and one-half cm below the septum there is a raised, opaque, white thickened patch on the endocardium 1 cm in diameter. The aortic valves are large, voluminous, but are stiffened at their bases by calcareous plaques. The cavity of the left ventricle is small and the wall is thickened, averaging 22 to 15 mm. The character of the muscle can no longer be made out. It is difficult to dissect out the coronary arteries, but at their orifices there is much calcification of the wall, which extends as far as they can be followed. The aorta at its base shows fairly large, opaque, yellow calcified plaques and in the ascending portion pin-head sized nodules of the same character. From the transverse arch, the aorta, as well as its main branches, is the seat of an extensive calcification and atherosomatous

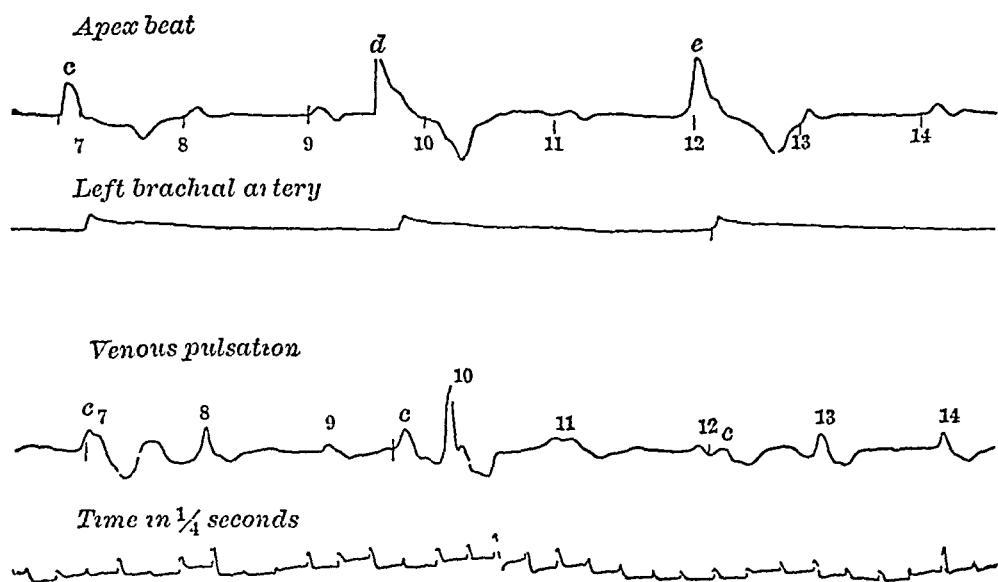


Fig 1.—From the case of complete heart-block, showing auricular systoles that are not transmitted to the ventricle. Auricular systoles, visible in tracings of both apex beat and jugular pulsations, are numbered 7 to 14, ventricular systoles lettered c, d, e (From Dr G C Robinson's article on Gallop Rhythm, Am Jour Med Sc, 1908, cxxxv, 870.)

ulceration, which increases until it reaches its maximum just above the bifurcation where the lining is composed of a thin layer of calcareous material broken and ulcerated in many places. Part of this breaking is, however, due to an attempt to open the vessel. At the transverse arch there is perhaps slight dilatation, which is also true of the thoracic portion, which measures 7.5 cm in circumference, the abdominal aorta measures 6.5 cm in circumference.

No attempt is made to dissect out the bundle of His, for it is not possible to see any gross change in the region of the course of the bundle which might affect its structure, and it is preserved intact for microscopical examination.

Histological Examination of the Auriculoventricular Bundle of His. A section of the heart septum to include the bundle of His was taken as follows. The upper border parallel to the auriculoventricular groove of the right side extending from

a position above the undefended space 2.5 cm in the direction of the coronary sinus, the lower border almost parallel to this, about 1 cm below the auriculoventricular groove or septum. This occurs as a sheet of loose fibrous tissue separating the delicate overhanging shell of the musculature of the right auricle from the right ventricular septum. The lateral borders of the section were cut perpendicular to the above. The middle leaflets of the tricuspid and aortic valves are cut away, so that only the stumps show in the sections. Serial sections were cut from below up almost parallel to the auriculoventricular groove. The plane of sectioning was taken with the posterior portion (i.e., that nearer the coronary sinus) somewhat nearer the groove than the anterior portion, so that allowing for the oblique course of the bundle of His from auricle to ventricle, some single sections would show the continuous course of the bundle from auricle to ventricle (i.e., in longitudinal section). If section is made parallel or perpendicular to the groove, the bundle is always shown in oblique or cross-section, and while its course can be traced, no one section shows it running from auricle to ventricle. Serial sections were made about 6 microns in thickness, but owing to the toughness of the tissue occasional sections were lost or had to be cut thicker. Two hundred and eighty seven sections were examined. Of every five slides, one was stained with hematoxylin and eosin, another with Mallory's connective-tissue stain. Subsequently the intervening slides were stained with hematoxylin and eosin. As the heart was fixed in formalin, the sections do not take the hematoxylin eosin stain as brilliantly as after fixation in Zenker's fluid.

Beginning in the auricle (i.e., the last section cut), No. 287 shows nothing but auricular musculature and the thick wall of the aorta. Lower down (No. 250) this is found merged with the fibrous tissue of the auriculoventricular septum and in the auricular fat and musculature near the septum appear the delicate interlacing fibers of Tawara's nodule. This seems to be quite normal, and is easily distinguishable from the coarser, straighter fibers of the auricular musculature. As the series is followed lower, small isolated masses of muscle tissue are found in the middle of the septum and fine delicate fibers approaching it from the ventricular side. At No. 190 in the series, the fibers from the ventricular side pierce the auriculoventricular septum and are in direct communication with Tawara's nodule. Following still lower, the septum intervenes between the auricle and the bundle, which is found cut in oblique section. This constituted the main bundle, as it lies between the pars membranacea and the ventricle before its division into the two ventricular branches. The fibers have the appearance characteristic of the bundle of His—much more slender and paler than the normal heart muscle, with striae faint or absent and nuclei more numerous. As is normally the case they are separated by loose connective tissue, but in some places there is also found between the fibers, apparently in the center of the bundle occasional small bands of fairly dense connective tissue, with frequent long cylindrical nuclei. This was not found in several normal bundles that I examined, though it was present in others and in some the loose type of connective tissue was greater than in the specimen of heart block.

The sections now begin to show some of the ventricular musculature with the stump of the tricuspid valve on the right side and of the aortic on the left. At No. 118 the bundle, apparently of smaller volume, divides into the two branches—that to the right side diving deep into the musculature and quickly being lost, that to the left being very superficial. The latter is separated from the musculature by a definite layer of fibrous tissue. Cut in cross section, it extends as a thin sheet over the surface. There is little detail to be made out, though large, pale, rather vesicular cells are found that suggest Purkinje fibers.

Thus the continuity of the bundle can be traced unbroken from Tawara's nodule to beyond its subdivision in the ventricles with no abnormality, other

than an occasional slight increase of connective tissue, no greater than is found in other hearts that have never exhibited any heart block.

Section from the left ventricle shows a marked increase of rather loose fibrous tissue, this is especially striking immediately beneath the endocardium, and does not bear any direct relation to the blood vessels. The heart-fibers are narrow, stain palely and in some cases are vacuolated with considerable peripolar pigment. On the edges of the fibrous areas or isolated in them, small atrophied muscular fibers are numerous.

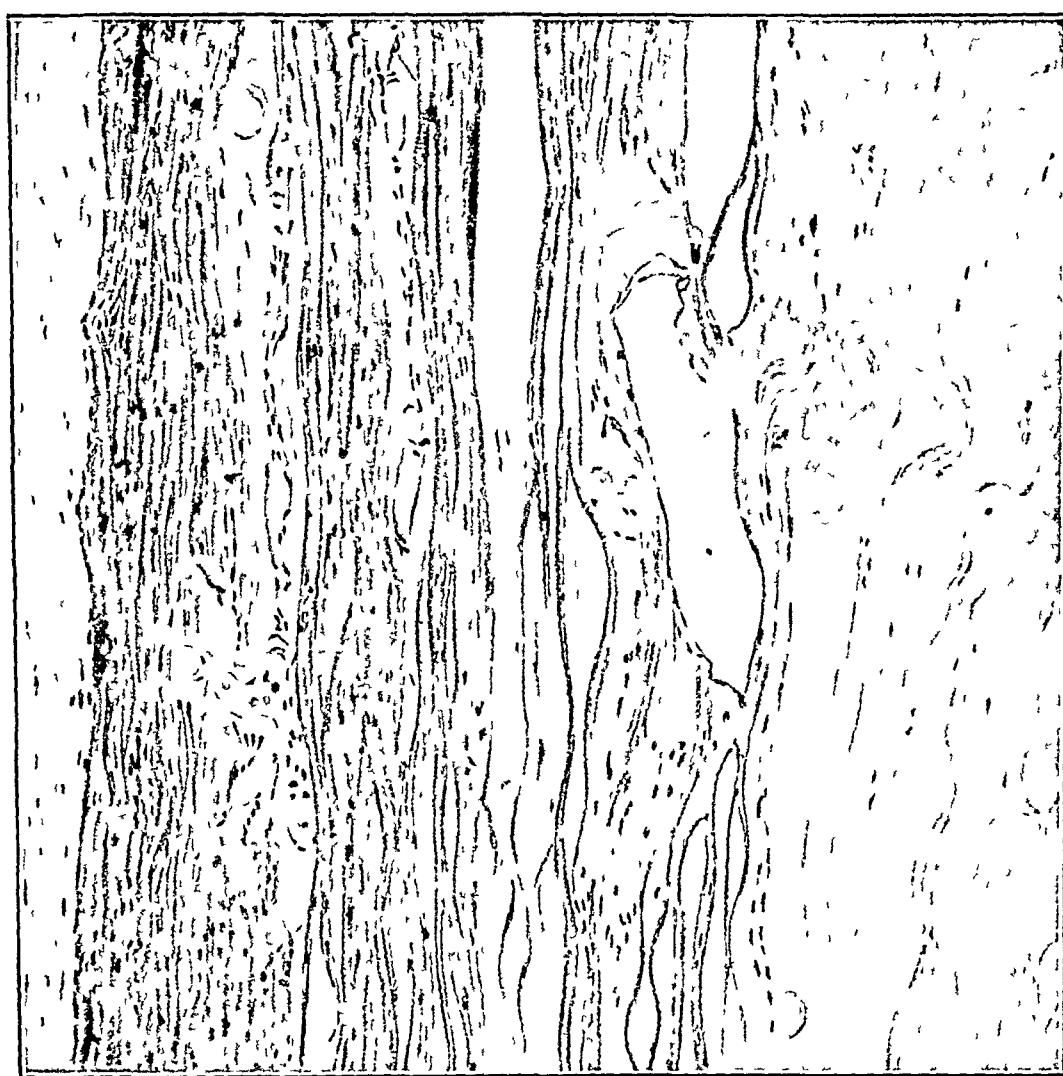


Fig. 2.—From the case of complete heart-block. Longitudinal section of the bundle of His in the ventricle before division into the two branches, showing practically no increase of connective tissue. Camera lucida, Zeiss Oc 2, Obj. A.

Section from the right ventricle shows less fibrous tissue, but still more than normal with broader, more normal muscle fibers. The spreading pale fibers, analogous to the Purkinje fibers, are well shown beneath the endocardium.

Section from the auricular septum shows much fat scattered between the muscle lobules and also between the individual fibers. The muscle fibers themselves are well preserved. In one place near the junction of the left surface of the

superior vena cava with the right auricle a circumscribed collection of about a dozen large ganglion cells were found.

Serial sections were also made through the sino auricular junction in the plane given by Keith to show the muscle fibers in which the heart beat is supposed by him to arise. Numerous continuous sections were found resembling fairly closely the appearance as given by Keith. The constant artery was found in its proper position just above the auricular musculature and around it a network of tissue easily distinguishable, grossly and microscopically, from the surrounding loose fibrous tissue. This network, which was in direct connection with thin bands of muscle in the wall of the base of the vein, apparently contains but little muscular tissue. It consists mainly of small isolated muscle fibers, cut obliquely and in cross section, surrounded by rather dense fibrous tissue. Several control series, with which I have compared it, all exhibit much less fibrous tissue and more muscle than does this series, and the muscle resembles strikingly the reticulated arrangement of Tawara's nodule. The significance of this fibrous change will be considered later.

Section from the aorta shows great localized thickenings of the intima, with increase of fibrous tissue in the media. Occasional rather extensive, circumscribed collections of small round cells are present in the outer layers of the adventitia.

Summarizing, we find a typical case of Adams-Stokes' syndrome with complete heart-block, known to have existed for at least five years. The permanent bradycardia was replaced by an even more marked paroxysmal bradycardia during the syncopal attacks. At autopsy a chronic myocarditis of the ventricles is found associated with a generalized sclerosis throughout the body. There is no gross lesion in the neighborhood of the bundle of His and microscopically the bundle can be traced in unbroken continuity from Tawara's nodule to a level in the ventricles well beyond its subdivision into two branches. Besides the fat lobules and loose connective tissue normally found in the bundle, there are here and there slight evidences of increase in connective tissue, but this is no greater than is found in the bundles of many hearts that have never shown heart-block. Fibrous changes are found in the muscle bundle described by Keith in the sino-auricular junction.

Shortly after the rediscovery of His' bundle in 1904 by Retzer<sup>3</sup> and Braunig,<sup>4</sup> Erlanger's<sup>5</sup> well-known experiments proved that both partial and complete heart-block could be produced by clamping the bundle with different amounts of pressure. After the proclamation of such an attractive hypothesis for the etiology of heart-block and Adams-Stokes' syndrome, it was but natural that much enthusiasm should be shown in hunting for supporting evidence in man. In this way a rapidly increas-

<sup>3</sup> Retzer Arch f Anat u Physiol, Anat Abt, 1904, p 1

<sup>4</sup> Braunig Arch f Anat u Physiol, Physiol Abt, 1904, p 1, Suppl

<sup>5</sup> Erlanger Bull Johns Hopkins Hosp, 1905, vii, 234, Jour Exper Med, 1905, viii, 676

ing number of cases of heart-block have been reported in which at autopsy lesions of the bundle of His were found. In a fairly large percentage of cases the lesions were gummatous, neoplastic, ulcerative or cicatricial and the bundle of His as well as a portion of the septum were unquestionably completely destroyed. In other cases, however, the lesion described was much slighter, and its causative relation to the heart-block does not seem

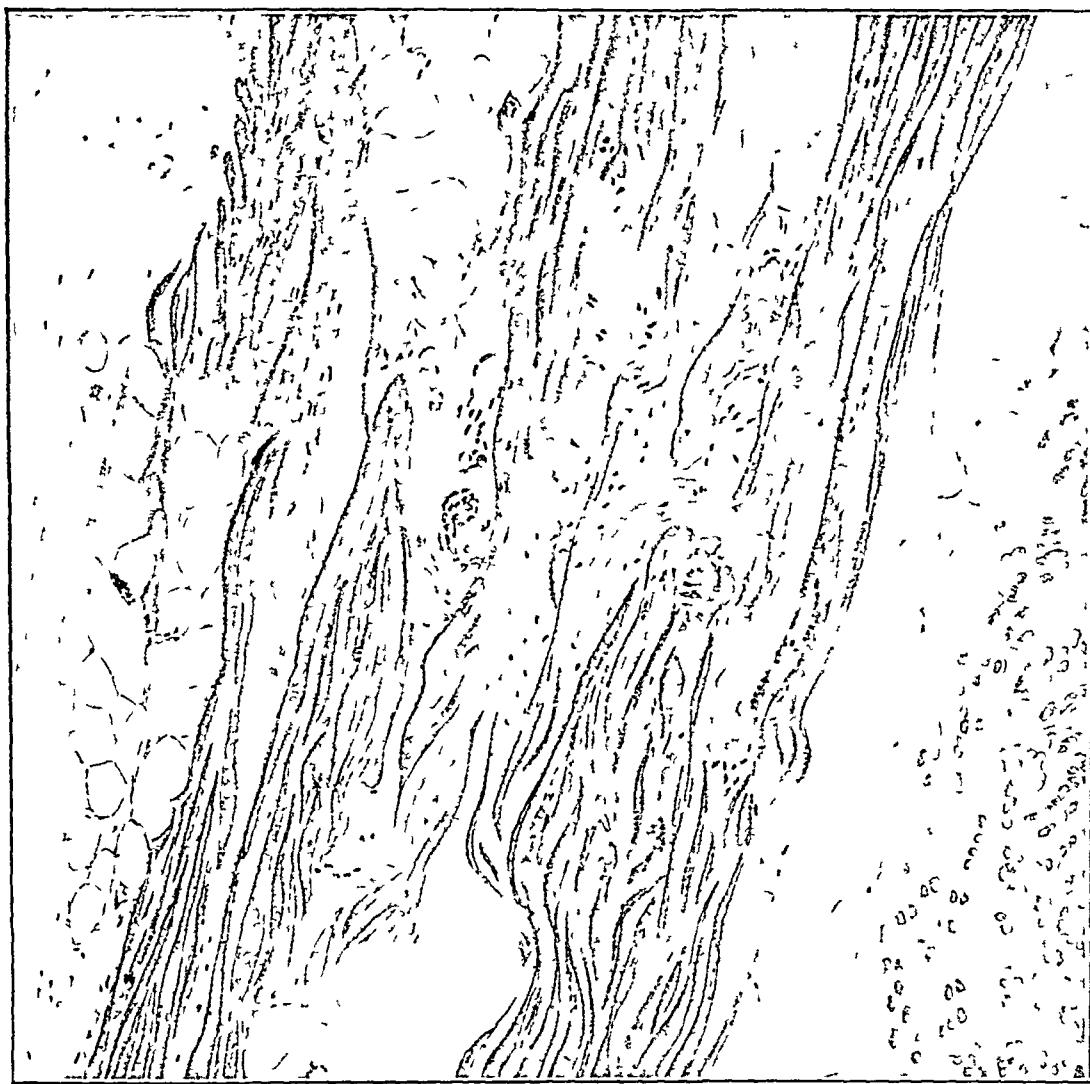


Fig 3.—Control from a case of normal rhythm. Bundle of His in same area as Figure 1, showing, if anything, more connective tissue. Camera lucida, Zeiss, Oc 2, Obj A.

conclusively proved. Such conditions are found as "the bundle has undergone considerable sclerosis," "tendency to fibrosis" or "more than half the cross-section of the bundle consists of connective tissue," or "the bundle showed fatty infiltration and degeneration." In these cases the possibility of other causes, such as lowered conductivity of

the anatomically unchanged muscle, changes in the nervous controlling mechanism, and so forth, cannot be excluded. Pertinent from this point of view is Lewis<sup>6</sup> apt comparison of the connection between auricle and ventricle to a train of gunpowder laid between two magazines.

Light the one end and you explode the other. Destroy half the thickness of the train by pouring water on it and the explosion travels equally well through the other half but if in destroying the first half you damp the second half, then the explosion will be delayed.

The auriculoventricular bundle not only contains more connective tissue than is found in the ventricles with a looser arrangement of muscle fibers but also its actual size varies considerably in different hearts. Incomplete lesions like those mentioned, therefore, are all the more difficult to interpret correctly, and it may fairly be said that in many of them the causative relation to heart-block is "not proven."

Cases of heart-block without any lesion of the bundle of His are much rarer. I have been able to find in the literature only two such cases, and even one of these is not absolutely clear. In the case reported by Deneke,<sup>7</sup> Fahsi<sup>8</sup> was unable to find any gross or microscopical lesion, but later states that in an abnormally long bundle the piece taken for section was so short that not all the bundle was examined, so that he could not definitely state that there was no lesion.

The second case reported by Nagayo<sup>9</sup> is much similar to the present one, except that the heart-block was incomplete and the clinical symptoms less severe and of shorter duration. At autopsy no lesion of the bundle was found, although there was an extensive ventricular myocarditis. Nagayo considers that the block occurred in this altered musculature, and on this assumption proposes a muscular type of heart-block (i.e., not in the auriculoventricular impulse-conducting mechanism). It is possible that the present case may belong to this class, but in this event the class must be extended to include complete block also. In a case of incomplete block Heineke, Mülle<sup>10</sup> and Hosslein<sup>10</sup> found a complete destruction of the bundle with replacement by scar tissue. They tried to explain the persisting functional connection between the two chambers by the assumption that during the gradual destruction of the bundle new minute muscular connections were formed between auricle and ventricle, or that previously unobserved minute bridges had taken on the function of transmitting the impulse.

6 Lewis Brit Med Jour., 1908, p. 1798.

7 Deneke Arch f klin Med., 1906, LXXXIV, 39.

8 Fahsi Vnichow's f path Anat., 1907, clxxviii, 562.

9 Nagayo Ztschr f klin Med., 1909, LVI, 495.

10 Heineke, Mülle<sup>10</sup> and Hosslein Deutsch Arch f klin Med., 1908, VIII, 459.



Fig. 4.—Sino auricular bundle of Keith and Flack. From the above case of complete heart block. Cross section of part of the wall of the superior vena cava showing one half of the sino auricular bundle in cross section. The artery which is constantly found in the center of the bundle is seen at the top of the picture with the fine reticulated muscle fibers of the sino auricular bundle about it. Some of the coarser auricular musculature is seen at the left of the picture. Camera lucida Zeiss Oc. 2 Obj. A



There have been several cases reported in which the heart-block has been temporary and followed by complete recovery. The most striking is that of Earnshaw,<sup>11</sup> in which a patient had two or three attacks of complete block, lasting several weeks and accompanied by symptoms of Adams-Stokes' syndrome, but terminating in an apparently complete recovery. The cause of the block was not ascertained. Some, for instance, Taylor's case,<sup>12</sup> due to intestinal toxemia, were evidently purely functional, others, occurring in the course of an acute infection such as rheumatism, probably were due to organic change. An interesting example of this kind is reported by Geihardt<sup>13</sup> the incomplete block with frequent syncopal attacks developed during an attack of acute articular rheumatism and acute pericarditis. With improvement in the malady the heart-block disappeared, but a few months later the patient contracted typhoid fever and died. At autopsy the auricle and ventricle were found to be normal, except that in the bundle of His there was a considerable round-cell infiltration with sclerosis of the vessel walls.

Magnus Alsleben<sup>14</sup> has recently reported numerous examples of temporary heart-block, occurring in the course of acute infections. Some were in cases of acute rheumatism and very probably underwent the same pathological course as the case just described. Another occurring in a fatal case of exudative pericarditis at autopsy showed no change in the bundle of His. In a convalescent pneumonia, incomplete block was produced by the use of digitalis, and, in fact, digitalis block has now become well recognized.<sup>15</sup>

All these observations tend to show that heart-block, even when complete, may not only be temporary, but may depend on a much more complex condition than a simple lesion or destruction of the bundle of His, and in the present case it is fair to assume that the cause of the complete auriculoventricular dissociation must be sought for elsewhere than in any morphological change of the muscular connecting mechanism. Where the cause does lie must remain a matter of conjecture, as in this case at least its site cannot be proved. Physiological changes, as, for instance a lowering of the conductivity of the bundle, might be possible, although they would hardly persist uninterruptedly for several years without

11 Earnshaw Paper read at Med Sect of Phila Coll of Physicians, Jan. 10 1910

12 Taylor, F. L. A Case of Transient Heart Block Due to Intestinal Toxemia. Jour Am Med Assn, 1908, L, 1246

13 Geihardt Deutsch Arch f klin Med 1908, xxiii 485

14 Alsleben, Magnus Ztschr f klin Med, 1909, lxix 82

15 For the literature on digitalis block, see Hewlett Jour Am Med Assn, 1907, xlvi, 47, Mackenzie Brit Med Jour 1905 pp 519 812, Rihl Ztschr f. Exper Path u Therap n p 74

organic lesion As it was impossible to examine the medulla and the vagi their possible influence also cannot be excluded The myocarditis, especially marked in the ventricles, or an unobservable change in the ultimate union of the connective mechanism with the ventricular wall, may have been sufficient to block the impulse after it had passed through the bundle, although both of these would necessitate a lesion over a wide-spread area

According to the latest researches, there is but little doubt that nerves accompany the muscle bundle Both Tawara<sup>16</sup> and Retzer<sup>9</sup> have spoken of the presence of nerves, but more recently Wilson<sup>17</sup> has demonstrated an extensive system of ganglion cells, nerve fibrils and plexuses that accompany the bundle from the auricle to the ventricle This discovery opens anew the whole question of neurogenic versus myogenic transmission of the nerve impulse, and, without entering into any discussion of this subject, it should be recognized that a lesion of the nervous mechanism must be considered a possible causative factor

Apropos of the fibrous changes in the bundle of Keith in the sino-auricular junction, Hering<sup>18</sup> has shown in dogs' hearts that section through the sulcus terminalis, cutting Keith's bundle, causes cessation of the heart-beat When the beat is resumed, if auricle and ventricle are both beating with their independent rhythm, a condition indistinguishable from heart-block is brought about Though it is not capable of proof, it may be that the fibrosis of Keith's bundle in the present case caused in this way a dissociation of auricular and ventricular beats rather than a failure of transmission of the impulse through the bundle of His Very recently Thorel<sup>19</sup> has stated that he has found a continuous set of muscular fibers joining Keith's sino-auricular node and Tawara's nodule, which resembles histologically their characteristic structure This, of course, was not investigated in the present case, as the sections had already been cut before the publication of Thorel's paper

As regards the nomenclature of the condition, there has been a tendency, especially among English and American writers, to confuse the terms "Adams-Stokes' syndrome" and "heart-block" This is unfortunate, not only because the former term should include the idea of syncopeal attacks and bradycardia, irrespective of dissociation of the auricles and ventricles, but also because the two distinguished physicians whose names it bears described conditions that are by no means necessarily

16 Tawara Das Reizleitungssystem d Säugetierherzens, Gustav Fischer, Jena, 1906

17 Wilson Proc Royal Soc, 1909, Ixxi, Series B, 151

18 Hering Munchen med Wehnschr, 1909, lvi, 845

19 Thorel Munchen med Wehnschr, 1910, lvii, 183



Fig. 5—Sino auricular bundle of Keith and Black. Control from the same area as Fig. 4 in a normal heart showing much more muscle tissue. Arrangement of tissue as before except that coarser auricular musculature is seen at the bottom of the picture. The rest of the reticulated muscle fibers was so great that 2 cm. of its lower portion has been omitted so that the coarser auricular fibers might be included in the picture. Camera lucida Zeiss Oc. 2 Obj. A

Figures 2, 3, 4 and 5 are by Hedwig Vogelsang



restricted to heart-block Adams<sup>20</sup> merely described a case of bradycardia with apoplectic seizures which at autopsy showed evidence of a fatty degeneration of the heart, and he undoubtedly knew nothing of the condition which we know as heart-block Stokes<sup>21</sup> monograph was entitled "Observations on Some Cases of Permanent Slow Pulse" Some of his cases reported were evidently cases of true heart-block in which he recognized the extra-auricular contractions and some were almost certainly not Since then the usual name given to it by French writers has been "pouls lent permanent, avec attaques épileptiformes," and, in fact, Charcot<sup>22</sup> thought that it was usually caused by lesions of the central nervous system, though he did not deny that the heart might in some cases be the seat of the trouble Huchard,<sup>23</sup> who suggested the name "Adams-Stokes' syndiome," considered it to be due to a sclerosis of the coronary and bulbar arteries, both helping to cause an anemia of the bulb, in other words, an intermittent claudication of the heart and medulla Whether true or not in the present case, it is an interesting coincidence that the patient suffered from a distinct intermittent claudication of one leg for several days before his death Various other extracardial causes have been suggested, supported by good pathological evidence Recently Pletnew<sup>1</sup> has suggested that the condition should be known as the "Morgagni-Adams-Stokes' syndrome" on account of two similar cases that the Italian anatomist<sup>24</sup> described

Without attempting to inquire too closely into the extracardial form of Adams-Stokes' syndrome, or intimating that the present case belongs to this class, a few evident examples of this form may be quoted as cases of Adams-Stokes' syndrome not caused by lesions of the bundle of His To be sure, they all occurred before the modern methods of investigating the pulse were in vogue, so that block cannot be absolutely excluded, but the nature of the cases fairly allow the assumption that it did not exist In the first place, there is Holberton's celebrated case,<sup>25</sup> in which, after an injury to the neck, there slowly developed an extreme bradycardia with fainting fits At autopsy the antero-posterior diameter of the foramen magnum was found much diminished with ankylosis between the atlas and skull and thickening of the dura and ligaments This caused compression and diminution in the size of the medulla and upper cervical

20 Adams Dublin Hosp Rep, 1827, iv, 396

21 Stokes Dub Quart Jour Med Sc, 1846, ii, 73

22 Charcot Leçons sur les maladies du système, nerveaux, 1872, ii, 140

23 Huchard Traité clinique des maladies du cœur, Paris, 1893, p 308

24 Morgagni. De sedibus et causis Morborum, Letter 9, Art 7, and Letter 62, Art 5

25 Holberton Med-Chir Tr, London, 1841, Series 2, vi, 76

cold. The heart was hypertrophied and dilated, but there was no gross lesion of the valves or septum. Another interesting case is that of Neuberger and Edinger,<sup>26</sup> in which a man having chronic constipation suffered from bradycardia and fainting spells occurring during defecation. He gave no clinical evidence of a heart lesion, and the pulse, never over 60, occasionally fell as low as 18, or for short periods stopped entirely. The autopsy, performed by Weigert, showed a normal heart, but remarkable changes in the cerebral nervous system. There was almost a complete absence of the right lobe of the cerebellum, and in the neighborhood of the decussation of the pyramids a small venous varix with beginning hemorrhagic infarction of the surrounding tissue. The explanation given of the paroxysmal bradycardia was that the straining at stool caused a congestion and thus pressure on the nuclei and roots of the vagus.

There is also evidence that stimulation of the peripheral vagus can cause bradycardia and fainting spells, though it is not definitely known whether or not this is accompanied by dissociation of auricle and ventricle. For instance, Hering and others have been able to cause the ventricle to drop beats by stimulating the vagus, whereas Erlanger considers that the vagus influences the ventricle entirely through the auricle. While taking cardiac tracings from one of his pupils, Thanhoffer,<sup>27</sup> by exerting digital pressure on both pneumogastries, caused not only extreme bradycardia, but a syncopal attack that lasted several minutes. In a case of bradycardia and arrhythmia without heart-block, Heineke<sup>10</sup> found that pressure always caused further slowing of the pulse and at one time a syncopal attack.

As it is an accepted fact that destruction of the bundle of His in the mammalian heart will cause heart-block and the symptoms of Stokes-Adams' syndrome, it seems proper to consider two main types—the neurogenic and the cardiogenic, the former producing a true bradycardia, the latter a heart-block, or dissociation of the auricles and ventricles. An attempt at further classification has been made by Nagayo<sup>9</sup> in subdividing the cardiogenic or heart-block into (a) *Reizleitung typus*, with complete heart-block, always caused by complete destruction of the bundle, and (b) muscular type with incomplete block accompanied by fatty degeneration, cellular infiltration of the bundle, and so forth. That these distinctions cannot always be maintained, however, is shown by various other observations as well as the present one.

26 Neuberger and Edinger Beil klin Wehnschr 1898 xxxv 69

27 Thanhoffer Centralbl f d Med Wissensch, 1875, viii, 405

## CONCLUSIONS

1 Adams-Stokes' syndrome and complete heart-block can exist uninterrupted for years with little or no lesion of the bundle of His

2 Whether the lesion in such cases may be in one or more different structures, and what those structures may be, or whether the difficulty is purely functional, has not yet been determined, but it is probable that there may in some cases be two or more contributing causes, both functional and organic

3 A possible explanation of the dissociation of auricle and ventricle in the present case may be that following a fibrosis of the sino-auricular bundle of Keith, the two chambers beat with independent rhythm rather than that the impulse was not properly conducted to the ventricle

My thanks are due to Dr W. T. Longcope for frequent help in the preparation of this paper

NOTE.—In most of the recent bibliographies of heart-block, Grunbaum's case of gumma of the intraventricular septum is misquoted as appearing in the *British Medical Journal*, 1906, 1, 378. These references have all been copied from Ewart's original quotation, which should read *Lancet*, London, 1906, 1, 378, appearing in the transactions of the West London Medical Society. By personal communication, however, I have just learned, since the corrected proofs for this paper were returned, that the heart is the same as that described by Keith and Miller, *Lancet*, London, Nov 24, 1906, and therefore should not be considered as a separate case in the literature.

# STUDIES OF BONE METABOLISM, ESPECIALLY THE PATHOLOGICAL PROCESS, ETIOLOGY AND TREATMENT OF OSTEOMALACIA<sup>1</sup>

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## 1 INTRODUCTION

Among the more frequently occurring pathological conditions to which human beings are subject, there are hardly any about which we know so little as those which may be roughly designated as chronic rheumatic conditions—a rather loose term used to include the various conditions known as osteo-arthritis, rheumatoid arthritis, osteitis deformans, arthritis deformans, chronic gout, rheumatic gout, chronic rheumatism, etc. And there are hardly any pathological conditions which have interested investigators in so many branches of medical science. Among clinical men investigations have been carried on not only by the internist, orthopedic surgeon and neurologist, who are constantly called on to treat symptoms due to these conditions, but also by men interested in such special branches, as, for example, the eye, some of whom maintain that many disorders of vision are closely bound up with certain of these rheumatic conditions. Investigations are being carried on constantly by pathologists and bacteriologists, and all of these conditions have been attributed, at one time or another, to certain bacteria. To show the interest taken in these diseases by those who concern themselves with the chemical side of pathological conditions, it is necessary only to mention the term "uric-acid diathesis." This term brings out again the relationships which these rheumatic disorders bear to widely different conditions in the minds of a large portion of the medical world, for diseases of nearly every organ of the body have been attributed to the uric-acid diathesis. Regarding the causes of these diseases, it may be said that there is probably scarcely any other group of conditions in the study of which so little progress has been made in the last century. In fact, in this matter, we are but little advanced beyond the old days when all diseases were attributed either to a "humor" circulating in the blood or to a "faulty diathesis."

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\* This paper was completed in its present form in December, 1908. Its publication was delayed by circumstances over which the author had no control.

<sup>1</sup> From the Department of Biological Chemistry of the Harvard Medical School

Several years ago Drs Goldthwait, Painter and Osgood of Boston made certain clinical and pathological investigations into some of these conditions, the results of which made it seem worth while to continue the work along chemical lines. The work was started with these investigators and later continued independently.\* After some preliminary urinary analyses, it seemed clear that if we were to learn anything about the processes taking place in the bone it would be necessary to make complete metabolism experiments in which the food, urine and feces might be analyzed quantitatively for calcium, magnesium, phosphorus, sulphur and nitrogen. As the amounts of these elements excreted, with the exception of nitrogen, are very small, it was evident that short experiments of a few days' duration would show nothing. But there were technical difficulties in the way which made such complete metabolism experiments lasting a week or more, practically out of the question if carried out by the usual methods. The amounts of most of these elements in different foodstuffs are so small that the analytical errors would be enormous, and, as each article of food would have to be analyzed, the time necessary for the analyses in connection with a single experiment would be practically prohibitive. These difficulties have probably been in large part responsible for our present ignorance regarding the metabolism of inorganic elements. The first step necessary, therefore, was to devise a method of carrying on metabolism experiments which would overcome these difficulties.

Such a method was devised and published<sup>1</sup>. The details will not be repeated here. It will suffice to say that a single sample well concentrated, dried, mixed and powdered, is finally obtained which represents the food of the whole experiment, thus making only single (or rather duplicate) determinations of each element necessary. Having obtained a method, it was necessary next to find proper cases on which to perform metabolism experiments.

Metabolism experiments were performed on a number of patients. Cases were plentiful, and our cases were carefully selected to represent distinct types of disease, and different stages of the same type. In some cases a second experiment was performed on a patient after the condition had changed. The patients were of both sexes and of widely differing ages and conditions of life. The conditions included rheumatoid arthritis, osteo-arthritis and osteitis deformans. Examination of the results disclosed some interesting facts. For example, in certain cases, accompanied by hypertrophy of the cartilage and atrophy of bone, there was a

\* A part of the expenses were contributed by the Proctor Fund for the Study of Chronic Disease.

<sup>1</sup> McCrudden, F. H. A New Technic in Metabolism Experiments, *Jour Med Research*, 1903, iv, 135

retention of sulphur, an element in which cartilage is comparatively rich, and a loss of calcium, an element in which bone is rich. These and other findings are discussed in the published papers,<sup>2</sup> and will therefore not be repeated here. They served to show the value of studies of this kind. But it was plain that before we could accurately interpret the results of such studies we must know more about the normal metabolism and more about the pathology of these diseases.

Later, I took up the work at this point. In the meantime, I was led by the wide-spread discussion of the uric-acid diathesis and the relation of uric acid to these diseases to study this side of the question. I undertook first the task of making as complete a study as possible of the literature on the subject. The task proved to be no light one as the literature is very much scattered. In fact, in all probability the reason that so much misinformation concerning uric acid prevails is that the many investigations on the different phases of the uric-acid question have not been collated. I felt therefore that I was doing a service in publishing the results of my study.<sup>3</sup> But while very interesting from the standpoint of pure biological chemistry, this study proved that we have not the slightest reason for believing that uric acid has anything to do with rheumatism. The idea that uric acid is responsible for these rheumatic conditions can be traced back to the Romans. The term "gout" comes from a Latin word "gutta," which expresses the idea of the Romans that the disease was due to a poison which separated out of the blood drop by drop into the joints. In the middle ages the poison or "humor" was variously called "black bile" or "tartar." It was referred to as the "materia peccans" by Sydenham. Some years after the discovery of uric acid in bladder-stones by Scheele<sup>4</sup> and Bergmann<sup>5</sup> in 1776, Murray Forbes<sup>6</sup> expressed the view that the substance was the "materia peccans," and the view was rendered more probable by the discovery of uric acid in gouty tophi by Wollaston.<sup>7</sup> When,

<sup>2</sup> Goldthwaite, J. E., Painter, C. F., and Osgood, R. B. The Preliminary Report of a Series of Metabolism Observations Made in Atrophic Arthritis, Hypertrophic Arthritis, Osteitis Deformans, and the Normal, *Am. Med.*, 1904, vii, 547, 590. Goldthwait, Painter, Osgood, and McCudden. A Study of the Metabolism in Osteomalacia, *Am. Jour. Physiol.*, 1905, xiv, 211. McCudden, F. H. The Effects of Castration on the Metabolism in Osteomalacia, *Am. Jour. Physiol.*, 1906, xvii, 211.

<sup>3</sup> McCudden, F. H. Uric Acid, the Chemistry, Physiology and Pathology of Uric Acid and the Physiologically Important Purin Bodies with a Discussion of the Metabolism in Gout, Boston, 1905, Fort Hill Press.

<sup>4</sup> Scheele, K. *Examen Chemicum Calculi Urinarii*, Opuscula, 1776, ii, 73.

<sup>5</sup> Bergmann, T. *Opuscula*, 1776, iv, 232.

<sup>6</sup> Forbes, M. A Treatise on gravel and Gout, London, 1793.

<sup>7</sup> Wollaston. On Gouty and Urinary Concretions, *Phil. Trans.*, London, 1797, 386.

In 1848, Gariod<sup>8</sup> found uric acid in gouty blood the matter was considered settled. The extension of the uric-acid theory to include all rheumatic diseases and many other pathological conditions is due chiefly to the writings of Alexander Haig of London, and is based on evidence that is not worthy of serious consideration. It can be seen that the idea is a direct inheritance of the ancient humoral pathology, only now, instead of "black bile" or "tartar," a definite chemical substance, uric acid, is the poisonous material. As I was interested more in bone metabolism than in uric-acid metabolism, I turned again to a study of the metabolism of the inorganic elements.

Fortunately, at this time, a moderately severe case of osteomalacia became available for study. Here was an opportunity to study a disease in which the chemical changes in the bone are much greater than in any other bone disease. Here, too, was a condition that had been much studied by pathologists, and in which the pathologists had come to two radically differing views concerning the process which is taking place. The view of Vinczow is based on the assumption that the inorganic part of bone is a dead material like the chitinous cuticula of crabs and certain insects undergoing no metabolism once it is laid down, and that of Cohnheim on the assumption that, at least well into adult life, bones are the seat of an uninterrupted and coincident apposition and resorption just as is the case in muscle or other tissues. As these two views embody fundamentally different concepts concerning bone metabolism, it was hoped that chemical studies might be of considerable value. A number of metabolism experiments on our patient and on animals, and analyses of normal and osteomalacic bones were therefore carried out. The results give a clearer insight into the process taking place in osteomalacia and enable us to decide between the two opposite views of the microscopists. In addition they throw considerable light on the subject of bone metabolism.

## 2 OSTEOMALACIA

### I HISTORICAL

Let us briefly consider what is known or believed concerning the etiology and the process taking place in osteomalacia. A detailed historical consideration of the different phases of the subject will be gone into where necessary later in the paper. At this point it will be necessary to point out only certain features as an introduction to my plan of experimental studies. The disease has been known for about a century

<sup>8</sup> Gariod A. Observations on Certain Pathological Conditions of the Blood and Urine in Gout, Rheumatism and Bright's Disease. Medico Chir. Tr. London 1848, xxxi, 83.

and a half Almost from the time the disease was first recognized, there was discussion concerning its identity with rickets But clinical and anatomical differences were soon observed which settled that question Whether or not the process going on in the two conditions is essentially the same is another question Early in the last century, microscopical and chemical examination of specimens of bone in this disease showed decalcification similar to that which takes place when dead bone is placed in dilute hydrochloric acid This appearance suggested that the condition was due to the action of an acid which dissolved the mineral constituents, leaving behind the soft osteoid tissue This view is the one taken by Lobstein, Virchow, and, in fact, most pathologists since These investigators consider the process in osteomalacia and in rickets essentially different, in that in osteomalacia, the lime-free bone is believed to be normal bone from which the inorganic constituents have been dissolved out by an acid, whereas, in rickets the lime-free bone is believed to be newly made bone free from inorganic material Cohnheim<sup>9</sup> was the first to express doubt concerning the correctness of Virchow's conception of the process According to Cohnheim, the bones, even in adults, are undergoing active anabolism and catabolism In osteomalacia, when bone is destroyed, organic substances as well as lime salts are taken up by the osteoclasts and then new bone made up of the organic matrix, but free from lime salts, is laid down just as in rickets Evidence supporting either of these two opinions was not available at the time Cohnheim wrote We can say, therefore, that until after 1889 nothing was known about the process taking place in osteomalacia except that the bones become poor in lime salts and that the decalcification begins at the inner surface of the bone and gradually reaches toward the middle of the cortex

In regard to the cause of the disease, hardly a guess was made until within twenty years Certain investigators stated that they found lactic acid in the urine of patients with osteomalacia—a finding which was used in support of Virchow's opinion that the process is one of halisteresis But even this, if true, did not go very deeply into the cause Since 1894, the disease has been very generally believed to be a disease of the ovaries, a belief due to the gynecologist, Fehling In 1879, another gynecologist, Fochier,<sup>10</sup> had removed the uterus and ovaries as a complement to a Cesarean section in a case of osteomalacia, and noting that the patient

9 Cohnheim, J. Lectures on General Pathology, Transl by A McKee, 1889, 1, 632

10 Fochier Sur les modifications récentes de l'opération césarienne, à propos d'un cas d'amputation utéro ovarienne comme complément de cette opération, Lyon méd, 1879, xxxi, 393, 473, 505, 545

promptly recovered from the osteomalacia, recommended that the operation be tried as a therapeutic measure Fehling<sup>11</sup> performed the operation on a number of patients, and, later, in a number of other cases, removed only the ovaries The operations were followed by very good results, and, as a result, Fehling expressed the opinion that osteomalacia was due to some disturbance in the functions of the ovaries It has been suggested by other writers that osteomalacia is a disease of the adrenals, and of the thyroid gland, but the view of Fehling that osteomalacia is a disease of the ovaries is at present the prevailing one

It will be seen that before the process taking place in osteomalacia can be described and the cause explained, a number of points must be settled We must know how the chemical composition of the bone in this disease differs from the normal, especially in its content of calcium, magnesium, phosphate, sulphur and nitrogen, and how the absorption and excretion of these elements differ from the normal in various stages of the disease We must know what evidence there is of the presence of acid in the tissues We must consider the evidence of histological examinations that have been made since Cohnheim wrote It will be necessary also to consider certain clinical factors concerning the occurrence of osteomalacia, its course without treatment and with various kinds of treatment, especially castration It will be necessary to consider the clinical effect, and the effect on the metabolism, of castration And, in addition, it will be necessary to consider certain other matters—the normal metabolism of inorganic elements, the artificial production of rickets and osteomalacia, the apposition of foreign elements by bone—matters that bear on the interpretation of my results These matters will be taken up in sequence, and the facts which I and others have established stated Finally, the various established facts will be brought together and an attempt made to describe the process, explain the cause and outline the treatment

## II THE PROCESS IN OSTEOMALACIA

### 1 *The Composition of the Bone in Osteomalacia*

A Inorganic and Organic Material Chemical analyses long ago showed that the amounts of mineral matter in the bone, and especially of the lime salts, were decreased in osteomalacia The earliest analysis, a

<sup>11</sup> Fehling, H Zehn Castrationen, Ein Beitrag zur Frage nach dem Werthe der Castration, Arch f Gynak, 1884, xxx, 441, Ueber Wesen und Behandlung der puerperalen Osteomalacie, Arch f Gynak, 1891, xxxix, 171, Weitere Beitrage zur Lehre der Osteomalacie, Arch f Gynak, 1895, xlvi, 472, Ueber Osteomalacie, Ztschr f Geburtsh u Gynak, 1894, xxx, 471

ough one of Bostock,<sup>12</sup> showed but 20 per cent of "earthy matter" in the bone in a case of this disease. But in this case, and also in the analyses of Marchand, Bogne, Ragsky and von Bibra, the authors did not report their results in such form that they can be compared with later results. That the proportion of inorganic matter is decreased and that of organic matter increased is shown by Tables 1 and 2, which show the percentage of each in the bone.

TABLE I—NORMAL BONE

	Inorganic	Organic
Fleisch*	65 9 70 2	29 8 34 1
Lehmann†	67 72	32 28
Zalesky‡	65 44	34 56
Langendorff and Mommsen§	54 24	45 76

\* Fleisch Ueber die Chemische Zusammensetzung der menschlichen Knochen, Ann d Chem u Pharm, xliii, 251

† Lehmann Ueber die chemische Zusammensetzung der Knochen, Schmidt's Jahrb, 1843, xxviii, 277

‡ Zalesky Ueber die Zusammensetzung der Knochen des Menschen und verschiedener Thiere, Med Chem Untersuch a d Lab zu Tübingen (Hoppe Seyler's), 1866, i, 19

§ Langendorff, O., and Mommsen J. Beiträge zur Kenntniss der Osteomalacie, Vincow's Arch f path Anat, 1877, lxix, 452

TABLE 2—OSTEOMALACIA BONE

	Inorganic	Organic
Duham	45 37	54 63
Huppert†	25 71	74 29
Moeis and Muck‡	38 23	61 77
Moers and Muck‡	35 11	64 89
Langendorff and Mommsen§	37 8	62 2

\* Duham, A. On Certain Abnormal Conditions of the Bones Guy's Hosp Reports, 1861, series 3, v, 348

† Huppert, H. Analyse eines osteomalacischen Knochens, Arch d Heilk, 1867, viii, 345

‡ Moeis and Muck Beiträge zur Kenntniss der Osteomalacie, Deutsch Arch f klin Med, 1869 v 485

§ Langendorff, O., and Mommsen, J. Beiträge zur Kenntniss der Osteomalacie, Vincow's Arch f path Anat, 1877, lxix, 452

To these results I can now add my own (Table 3), which shows the amounts of lime, magnesia and phosphoric acid in the bone. From these results it is clear that the relative amount of inorganic matter is decreased and the amount of organic matter increased in osteomalacia.

12 Bostock, J. Analysis of the Bones of the Spine in a Case of Mollities Ossium Med Chir Tr, 1819 iv 38

TABLE 3—PERCENTAGE OF INORGANIC MATTER IN THE DRIED BONE

	Normal	Osteomalacia
Human <sup>*</sup>	48.54	28.02
Horse†	56.74	35.61

\* McCrudden, F. H. The Chemical Analysis of Bone from a Case of Human Adolescent Osteomalacia. *Jour Biol Chem.* 1910 vii, 199.

† McCrudden, F. H. The Composition of Bone in Osteomalacia, Am Jour Physiol., 1906, xviii, 32.

TABLE 4—PERCENTAGE OF CALCIUM OXID IN THE DRIED BONE

	Normal	Osteomalacia
Moers and Muck		17.36
Moers and Muck		18.07
McCrudden†	28.85	15.44
McCrudden (horse)‡	33.30	19.22

\* Moers and Muck Beiträge zur Kenntniss der Osteomalacie, *Deutsch Arch f klin Med.*, 1869, v, 485.

† McCrudden, F. H. *Jour Biol Chem.*, 1910, vii, 199.

‡ McCrudden, F. H. Am Jour Physiol., 1906, xviii, 32.

B Calcium The calcium in the dried bone is decreased to nearly one-half its normal value in these cases. From Table 5 it will be seen that not only the amount of calcium in the whole bone, but also the amount in the ash is decreased to some extent. In other words, the relative amount of the other mineral constituents of the ash is increased.

TABLE 5—PERCENTAGE OF CALCIUM OXID IN THE BONE ASH

	Normal	Osteomalacia
Zalesky <sup>*</sup>	52.64	53.06
Langendorff and Mommsen†	53.05	44.48
Gabriel‡	51.31	
Huppert§		45.41
Moers and Muck¶		45.47
Moers and Muck¶		50.66

\* Zalesky Med.-chem Untersuch a d Lab zu Tübingen (Hoppe-Seyler's), 1866, i, 19.

† Langendorff and Mommsen *Viechow's Arch f path Anat.* 1877, lxix, 452.

‡ Gabriel, S. *Chemische Untersuchungen über die Mineralstoffe der Knochen und Zahne, Ztschr f physiol Chem.*, 1894, xviii, 257.

§ Huppert *Arch d Heilk.* 1867 viii, 345.

¶ Moers and Muck *Deutsch Arch f klin Med.*, 1869 v 485.

TABLE 6—PERCENTAGE OF PHOSPHORUS PYROXID IN THE DRIED BONE

	Normal	Osteomalacia
Moers and Muck		18.20
Moers and Muck		14.38
McCrudden†	19.55	12.01
McCrudden (horse)‡	23.44	16.28

\* Moers and Muck *Deutsch Arch f klin Med.* 1869 485.

† McCrudden, F. H. *Jour Biol Chem.* 1910 vii, 199.

‡ McCrudden, F. H. Am Jour Physiol., 1906, xviii, 32.

C Phosphate The amount of phosphate is decreased. On comparing Tables 4 and 6 it will be seen that the decrease in phosphate was only

to about two-thirds the normal, whereas the decrease in calcium in the same cases was to nearly one-half the normal. In other words, the ratio  $P_2O_5 : CaO$  in the bones in osteomalacia is greater than the normal ratio.

TABLE 7—PERCENTAGE OF PHOSPHORUS PENTOXID IN THE ASH

	Normal	Osteomalacia
Zalesky*	38 49 39 02	
Langendorff and Mommsen†	43 93	34 76
Gabriel‡	36 65	
Huppert§		39 26
Moers and Muck		47 67
Moers and Muck		43 00
“ Zalesky Med -chem Untersuch a d Lab		zu Tubingen (Hoppe Seyler's), 1866, 1, 19
† Langendorff and Mommsen Virchow's Arch f path Anat, 1877, lxix, 452		
‡ Gabriel Ztschr f physiol Chem, 1894, xviii, 257		
§ Huppert Arch d Heilk, 1867, viii, 345		
Moers and Muck Deutsch Arch f klin Med, 1869, v, 485		

The results here are rather variable. On comparing Tables 6 and 7, it will be seen that although the amount of phosphate in the dried bone is decreased to about two-thirds the normal, that in the ash is nearly unchanged. In other words, the decrease in the amount of calcium in the ash is partly made up by an increase in the relative amount of phosphate.

TABLE 8—PERCENTAGE OF MAGNESIUM OXID IN THE DRIED BONE

	Normal	Osteomalacia
Moers and Muck*		0 484
Moers and Muck*		0 902
McCradden†	0 14	0 57
McCradden (horse)‡	0 105	0 48
* Moers and Muck Deutsch Arch f klin Med, 1869, v, 485		
† McCradden, F H Jour Biol Chem, 1910, viii, 199		
‡ McCradden, F H Am Jour Physiol, 1906, xvii, 32		

D Magnesium The amount of magnesium is increased. This, taken in connection with the other results, means that the ratio of the magnesium phosphate to that of the calcium phosphate is increased over the normal. From this alone we would be strongly inclined to reject the theory that the process in osteomalacia is one of simple halisteresis comparable with the action of an acid. It would be difficult to imagine how an acid could dissolve the calcium phosphate and leave the more soluble magnesium phosphate undissolved. Furthermore, if we could imagine such a condition, then, when the calcium was decreased in amount to one-half the normal, the relative amount of magnesium would be only doubled. But our tables show an increase of the magnesium of more than fourfold, which means that there is an increased deposition of magnesium, and

strongly suggests that the magnesium is used in part to supply the deficiency in calcium. The ash analyses bring this point out again. Certain investigators have reported these results in the form of magnesium phosphate. Table 10 brings out the great increase in magnesium even more than the other tables.

TABLE 9.—PERCENTAGE OF MAGNESIUM OXID IN THE BONE ASH

	Normal	Osteomalacia
Zalesky*	0.405	0.521
Gabriel†		0.77
Huppert‡		4.46
Moers and Muck§		1.267
Moers and Muck§		2.528

\* Zalesky Med.-chem Untersuch a d Lab zu Tübingen, 1866, I, 19

† Gabriel Ztschr f physiol Chem., 1894, xvii, 257

‡ Huppert Arch d Heilk., 1867, viii, 345

§ Moers and Muck Deutsch Arch f klin Med., 1869, v, 485

TABLE 10.—PERCENTAGES OF MAGNESIUM PHOSPHATE IN BONE ASH

	Normal	Osteomalacia
Gorup-Besanez*	1.04	
Gegenbauer†	1.75	
Huppert‡		9.6
Chabrié§		26.9

\* Gorup-Besanez Lehrbuch der Chemie, 1874, III

† Gegenbauer Anatomie des Menschen, 1883, p. 98

‡ Huppert Arch d Heilk., 1867, viii, 345

§ Chabrié Les phénomènes chimiques de l'ossification, Paris, 1895, p. 65

TABLE 11.—PERCENTAGE OF SULPHUR IN THE DRIED BONE

	Normal	Osteomalacia
McCradden*	0.14	0.55
McCradden (horse)†	0.10	0.37

\* McCradden, F. H. Jour Biol. Chem., 1910, vii, 199

† McCradden, F. H. Am. Jour. Physiol., 1906, xvii, 32

E. Sulphur These results are of special interest. The organic matrix of bone is made up largely of glycoproteins which, compared with most other proteins, are rich in sulphur, so that we should expect in osteomalacia, in which the percentage of organic matter is increased, to find an increased amount of sulphur. But, if the process were a halisteresis, similar to that which takes place when bone is placed in acid, we should expect in cases like the two which we studied, in which the calcium had decreased to nearly half its normal value, to find the amount of sulphur correspondingly nearly doubled, whereas it has increased in both cases nearly fourfold. This, again, as in the case of magnesium suggests that

there is an apposition of new tissue, in this case an apposition of tissue similar to the organic matrix of normal bone

**Summary of Results of Bone Analyses** To summarize the results of the bone analyses, we can say that in osteomalacia the proportion of inorganic constituents is decreased and the proportion of organic constituents increased. The decrease in the proportion of inorganic constituents is due to a loss of calcium phosphate. The proportion of magnesium phosphate and of the organic matrix of bone is increased. The increase is greater than can be accounted for by simple decalcification, so that we must assume that it is due to material newly laid down to replace the calcium phosphate. These findings are in accord with Cohnheim's theory, and lend considerable weight to it, and cannot be explained by the theory of halisteresis.

## 2 Metabolism Experiments in Osteomalacia

If, as the bone analyses seem to indicate, the catabolism of calcium is increased and the apposition of magnesium and material rich in sulphur increased, we might expect examination of results of metabolism experiments in the active period of the disease to show a disturbance of the equilibrium in the case of these elements. Moers and Muck,<sup>13</sup> Schmuziger,<sup>14</sup> Fehling,<sup>15</sup> Denecke<sup>16</sup> and Schuchardt<sup>17</sup> made quantitative determinations of the calcium in the urine in osteomalacia, but, since calcium is excreted chiefly in the feces, and these investigators examined neither food nor feces, their results are of little value. At this point, also, we shall not consider the studies carried on when the patient was recovering, either as the result of castration or other treatment, or the case of one patient who was far advanced in pregnancy, or the case of one patient who had suffered many years and was so severely afflicted that castration did not afford even temporary relief. A consideration of the stage of the disease in comparing the results of the metabolism experi-

13 Moers and Muck Beitrage zur Kenntniss der Osteomalacie, Deutsch Arch f klin Med., 1869, v, 485

14 Schmuziger, F Zur Urinuntersuchung bei puerperaler Osteomalacie, Centralbl f d med Wissenschaft, 1875, xiii, 946

15 Fehling, H Ueber Wesen und Behandlung der puerperalen Osteomalacie, Arch f Gynak., 1891, xxxix, 171

16 Denecke, H Ueber das Verhalten der Kalk und Phosphorsaureauscheidung im Harn Osteomalacischer vor und nach der Castration, Inaug Diss., Wurzburg, 1896

17 Schuchardt, L Quantitative Bestimmung von Kalk- Magnesia- und Phosphorsaureausscheidung im Harn Osteomalakischer vor und nach den therapeutischen Eingriffen Inaug Diss., Wurzburg, 1897

ments is an important matter, and will be returned to later. A failure to do this accounts for the apparently contradictory results which certain investigators obtained.

TABLE 12.—SUMMARY OF THE RESULTS OF COMPLETE METABOLISM EXPERIMENTS ON PATIENTS WITH ACTIVE OSTEOMALACIA

Experimenter	Duration of Expt Days	Weight of CaO in Food	Weight of CaO in Excreta	Loss of CaO
Limbeck*	5	2 965	5 604	2 642
Korczynski†	4			loss of CaO
His‡	11	8 66	9 48	0 82
His‡	7	6 08	7 24	1 16
Neumann§	5	11 26	11 65	0 39
Hotz	8	10 78	12 73	1 95
Goldthwait, Painter, Osgood and McCrudden**	8	4 56	5 66	1 10
McCrudden††	6	3 44	8 27	4 83

\* Limbeck, R von Zur Kenntniss des Osteomalacie, Wien med Wehnschr, 1894, xliv, 737, 743, 844

† Korczynski, L von Zur Kenntniss des Stoffwechsels bei Osteomalacie, Wien med Presse, 1902, xliii, 1073, 1131, 1117, 1228, Zwei Stoffwechselversuche bei Osteomalacie, Centralbl f Stoffwechsel u Verdauungskr, 1902, iii, 61

‡ His Zur Phosphortherapie bei Osteomalacie, Deutsch Arch f klin Med, 1902, lxxiii, 546

§ Neumann, S Weiterer Untersuchungen über die Stoffwechselverhältnisse des Calciums, Magnesiums, der Phosphorsäure und des Nitrogens bei puerperaler Osteomalacie, mit besonderer Berücksicht auf die durch die Castration und andere therapeutische Eingriffe verursachten Veränderungen des Stoffwechsels, Arch f Gynak, 1896, h, 130

|| Hotz, G Phosphorsäure- und Kalkstoffwechsel bei Osteomalacie unter dem Einfluss der Phosphortherapie, Ztschr f exper Path und Therap, 1906, iii, 605

\*\* Goldthwait, Painter, Osgood and McCrudden Am Jour Physiol, 1905, xiv, 211

†† McCrudden, F H Am Jour Physiol, 1906, xvii, 211

A Metabolism of Calcium It will be seen from Table 12 that there is always a loss of calcium by the body, a result which is in accord with the low calcium content of the bones in this disease.

B Metabolism of Phosphorus Studies of the phosphorus metabolism have given variable results. Later, after we have considered the calcium metabolism in different stages of the disease, the reason for the variable results will be clear.

TABLE 13.—MAGNESIUM OXID IN THE FOOD AND EXCRETA

Investigator	Duration Days	Food	Excreta	Retention
Goldthwaite, Painter, Osgood and McCradden*	8	2 207	2 015	0 192
*Am Jour Physiol, 1905, xiv, 211				

C Metabolism of Magnesium Corresponding with the increased content of magnesium in the bone in osteomalacia, we find (Table 13) that the body is retaining magnesium

TABLE 14—SULPHUR IN THE FOOD AND EXCRETA

Investigator	Duration Days	Food	Excreta	Retention
Goldthwaite, Painter, Osgood and McCradden*	8	7 15	2 68	4 47
*Am Jour Physiol, 1905, xiv, 211				

D Metabolism of Sulphur Here, again (Table 14), as in the case of magnesium, we find a retention corresponding with an increased amount of the element in the bone

E Metabolism of Nitrogen In our experiments and in those of von Korczynski, there was always retention of nitrogen

Summary of the Results of Metabolism Experiments To summarize briefly the results of the metabolism experiments, we find that the body is losing calcium and retaining magnesium and sulphur. These results are in accord with those obtained by bone analyses and confirm the supposition that in osteomalacia the process is not one of simple passive halosteresis, but an active one of increased bone metabolism. Old bone is destroyed and new bone laid down. But the new bone is similar to the organic matrix of normal bone and is free from, or poor in, calcium phosphate, instead of which there is a partial replacement of the calcium phosphate by magnesium phosphate<sup>18</sup>

### 3 The Results of Pathological Investigations

The question next to be answered is whether or not histological investigations offer anything in support of our chemical investigations. If we examine rachitic bones, we find osteoid tissue at the junction of epiphyses and diaphyses, as well as beneath the periosteum, that is, the organic matrix of bone without the lime salts. If we examine the bone in osteomalacia, we find similar osteoid tissue, but not, as in rickets, beneath the periosteum and at the boundaries of epiphyses and diaphyses, but in the interior of the bone in proximity to the Haversian canals. Yet, in the former case, this osteoid tissue is considered new lime-free bone, and, in the latter case, old decalcified bone. There was no good reason for this assumption, except that the bone when once laid down was supposed to be dead tissue not undergoing metabolism—a point which will be discussed later. I have already referred to Cohnheim's opinion that the process

<sup>18</sup> This matter of the substitution of magnesium phosphate for calcium phosphate will be further discussed later.

in osteomalacia is not one of halistasis, but is essentially the same as that in rickets. The statement that Cohnheim makes<sup>19</sup> is that whenever bone disappears Howship's lacunæ are at once formed and filled with osteoclastic giant cells that take up organic ground substance as well as the mineral constituents, and that the osteogenic zones must have originated by apposition. He admits that the minutiae of the process are completely unknown, but states that at no stage does an osteoid tissue free from lime occur. Cohnheim could not adduce good evidence in favor of his opinion. Certain microscopical observations concerning bone changes have since been made, however, which have an added interest in view of the chemical findings.

The important finding in these histological investigations was an abundance of osteoblasts in the osteoid zones of the bones in osteomalacia. Von Recklinghausen<sup>20</sup> especially made a very interesting and exhaustive report on the histology of osteomalacia and certain other similar conditions. He called attention to the abundance of osteoblasts and Sharpey's fibers, and to the "youthful appearance," as he calls it, of many of the bone corpuscles as evidence that the osteoid tissue is new tissue. He refers also to the fact that patients with osteomalacia often start a good callus formation. It may not be amiss here to refer to his statement regarding the similarity of the histological appearance in osteitis deformans and osteomalacia. In fact, he regards osteitis deformans as a local osteomalacia. As a result of increased metabolism at one place, the bone at this place remains uncalcified for a time, in consequence of which the characteristic bending occurs. The results of one experiment which we performed on a patient with osteitis deformans are in accord with this view.<sup>21</sup> Tachiro,<sup>22</sup> too, has observed the abundance of osteoblasts in the osteoid tissue in osteomalacia, and notes the fact that this osteoid tissue is contiguous to and continuous with young proliferating endosteum, and that the new formation of osteoid tissue is parallel with the disappearance of old bone. He, too, confirms the observations of von Recklinghausen regarding the similarity in the process of osteitis deformans and osteomalacia. Hanau's discovery,<sup>23</sup> which will be referred to again, that, in many cases of preg-

19 Cohnheim, J. *Lectures on General Pathology*, Transl. by A. McKee, 1889, 1, 632.

20 Recklinghausen, F. von. *Die fibrose oder deformirende Ostitis, die Osteomalacie und die osteoplastische Carcinose in ihren gegenseitigen Beziehungen*, Fest-schr. Rudolph Virchow zu seinem 71 Geburtstage gewidmet, Berlin, 1891.

21 Goldthwait, Painter and Osgood. *Am Med.*, 1904, viii, 547, 590.

22 Tachiro, Y. *Histologische Untersuchungen an osteomalacischen Knochen*, Beitr. z. path. Anat. u. z. allg. Path., 1903, xxiv, 220.

23 Hanau, A. *Ueber Knochenveränderungen in der Schwangerschaft und über die Bedeutung des puerperalen Osteophyts*, Fortschr. d. Med., 1892, 1, 237.

nant women with apparently sound bones during life, post-mortem examination showed an appearance similar to osteomalacia, especially in the bones of the pelvis, is in accord with the view that the osteoid tissue is new tissue, for he too found osteophytes in this tissue. The histological investigations, then, are in accord with the chemical in indicating that the process in osteomalacia consists in a replacement, by new calcium-free or calcium-poor bone, of normal bone that has undergone catabolism.

My conclusions regarding the process in osteomalacia may in part explain the controversy regarding infantile osteomalacia. Rehn,<sup>24</sup> especially, has reported certain cases which he differentiated from rickets and called infantile osteomalacia. In this diagnosis he was confirmed by von Recklinghausen. But Ziegler<sup>25</sup> disputed this diagnosis and called the cases rickets. It may well be that in a severe enough case of rickets not only may the body fail to supply lime salts to parts of the bone which should calcify, but may also destroy bone which has already become calcified and lay down new osteoid tissue instead.

#### *4 Metabolism in Normal Bones*

All the evidence concerning osteomalacia so far considered points toward the conclusion that in this disease the catabolism of bone is increased, and that the body fails to respond with an apposition of normal bone. It is worth while at this point to consider what other evidence there is that the mineral constituents of the bone are capable of undergoing metabolism. In the first place, it may be stated that the view that the mineral constituents of the body are dead and not a part of the living body and undergoing metabolism, is a remnant of the old view that there is a sharp distinction between the living or organic elements or compounds and the inorganic, a view long since disappeared. We do not have any difficulty in understanding that the small amounts of calcium, magnesium and iron in the blood or muscles are used up and have to be renewed—in other words, undergo metabolism, and it is difficult to understand why the pathologists who took Virchow's view could find difficulty in believing that the mineral salts of the bone undergo metabolism. If the muscle cells, with their fraction of 1 per cent of mineral salts undergo metabolism, then why not also the bone cells with their 50 or 60 per cent mineral salts? We have no difficulty in understanding that the material of the blood plasma or the connective tissue or neuroglia fibrils must be renewed.

<sup>24</sup> Rehn Ein Fall von infantiler Osteomalacie, Jahrb f Kinderh., 1878, new series, XII, 100, Ueber Osteomalacie im Kinderalter, Jahrb f Kinderheilkunde, 1883, new series, XIX, 170.

<sup>25</sup> Ziegler Lehrbuch der speciellen pathologischen Anatomie, Ed 6, 1890, Jena, p 123.

Why should there be any difficulty in understanding that the quite analogous bone should be renewed? *A priori*, then we should say that bone normally undergoes metabolism. But there is more direct evidence of both bone anabolism and bone catabolism.

When a fracture occurs, we have evidence of new bone formation in the formation and subsequent calcification of the callus, and in starvation we have evidence of bone destruction. Thus it was shown that the professional fasters, Cetti and Breithaupt, after a week to ten days of starvation, were excreting nearly as much calcium per day as in the beginning.<sup>26</sup> The amount of flesh catabolized could be calculated from the amount of nitrogen excreted and, the amount of calcium in flesh being known, it could be shown that the amount lost was much more than could be accounted for unless it was assumed that the calcium in the bones was undergoing catabolism. This is likewise true of Munk's experiment on dogs.<sup>27</sup> Forster<sup>28</sup> fed a dog a diet poor in calcium for twenty-six days. In that time, the dog lost 13.57 gm. calcium over and above that taken in the food. By analysis of the different organs, Forster showed that this must have come chiefly from the bones. Besides the metabolism experiments, we have direct analyses of the bones showing that the mineral constituents are used up during starvation. Voit's<sup>29</sup> experiments which were the first to show that the bones lose weight during starvation, can not be used as evidence because he did not show that the mineral constituents decrease. Weiske's<sup>30</sup> negative results in the case of starving dogs are likewise not conclusive on account of the shortness of the experiments (seven to eleven days). Sedlmair's experiments are interesting and conclusive.<sup>31</sup> This author starved cats for a month or more, analyzed the excreta, and, at the end of the period, analyzed the bones of the cat and compared the results with those of normal cats.

<sup>26</sup> Lehman, C., Mueller, F., Munk, I., Senator II., and Zuntz, N. Untersuchungen an zwei hungernden Menschen, Vinchow's Arch f path Anat, 1893, cxxx, (Supplementheft)

<sup>27</sup> Munk, I. Beitrage zur Stoffwechsel- und Ernahrungslehre, Arch f d ges Physiol (Pflüger's), 1894, lviii, 309

<sup>28</sup> Forster Ueber die Verarmung des Körpers, speciell der Knochen an Kalk bei ungenugender Kalkzufuhr, Ztschr f Biol, 1876, viii, 464

<sup>29</sup> Voit, C. Ueber die Verschiedenheit der Eiweissersetzung beim Hunger, Ztschr f Biol, 1866, ii, 307

<sup>30</sup> Weiske, II. Ueber den Einfluss der Nahrungsentziehung auf das Gewicht und die Zusammensetzung der Organe insbesondere der Knochen und Zahne, Ztschr f physiol Chem, 1896-7, xxi, 485

<sup>31</sup> Sedlmair, A. Ueber die Abnahme der Organe, insbesondere, der Knochen, beim Hunger, Ztschr f Biol, 1899, xxviii, 25

The amount of calcium excreted which came from bone was equivalent to 1 per cent per day of the total bone of the cat, a confirmation of the results of Munk and Forster. But Sedlmair showed in addition by bone analyses that there was a loss of from 4.6 to 13.8 per cent of the ash and from 2.5 to 11.6 per cent of the calcium oxid of the bones. In one cat there was a loss of 13.8 per cent ash, 11.6 per cent calcium oxid, and 12.8 per cent ossein—results which are close enough to suggest that the organic and inorganic materials of the cell were destroyed together. Studies of the calcium metabolism, then, indicate that the bone is constantly undergoing metabolism.

Studies of the phosphate metabolism lead to the same conclusion as studies of the calcium metabolism. It is commonly stated that the excretion of nitrogen and phosphorus are nearly parallel, that the ratio N:P in the excreta is almost constant and, on the average, is about the ratio in which these elements occur in flesh, so that theoretically the phosphorus excretion might be roughly used as a measure of protein metabolism. This belief is probably based on the statement of Zuelzer,<sup>32</sup> who came to such conclusions as a result of his work. His own tables on which he bases his conclusions do not show such constancy but, on the contrary, show great variation in the ratio. More recent experiments<sup>33</sup> show that the phosphorus and the nitrogen excretion vary quite independently even on a constant diet,<sup>34</sup> and the amount of phosphorus metabolized may be much greater than could come from the flesh metabolized. Determinations of the ratio of nitrogen to phosphorus in different tissues have been made,<sup>35, 36</sup> so that from the amount of nitrogen excreted in starvation we can tell the maximum amount of phosphorus corresponding if neither bone nor nervous tissue were destroyed. This has been done,<sup>36, 37</sup> and there was always a great excess of phosphorus that must have come chiefly from the bones since it has been shown that the dry brain and cord, the other phosphorus-rich tissues, do not lose weight.

32 Zuelzer, W. Ueber das Verhaltniss der Phosphorsaure zum Stickstoff im Urin, Virchow's Arch f path Anat., 1876, pp 66, 223, 282

33 Buchmann, L. Beitrage zum Phosphorstoffwechsel, Ztschr f diatet u physik Therap., 1904-5, viii, 66

34 Kellar, A. Phosphor und Stickstoff im Sauglingsorganismus, Arch f Kinderh., 1900, xxix, 1

35 Cronheim, W., and Muller, E. Versuche über den Stoff- und Kraftwechsel des Sauglings mit besonderer Berücksichtigung des organisch gebundenen Phosphorse, Ztschr f diatet u physik Therap., 1902, vi, 25, 92

36 Munk, I. Beiträge zur Stoffwechsel- und Ernährungslehre, Arch f d ges Physiol (Pfluger's), 1894, lviii, 309

in starvation.<sup>29</sup> Calculation from the data of older results, for example, those of Forster,<sup>38</sup> show the same result. We can say then that the bones, including the mineral constituents, are undergoing metabolism constantly.

### *Summary Concerning the Process in Osteomalacia*

To sum up our conclusions concerning the process in osteomalacia, we may say that experiment has shown that the bones are normally undergoing metabolism—*are* being built up and destroyed like other tissue. This is so in infants and as the uncalcified parts of the bone are gradually destroyed the new bone laid down to replace them is richer in lime salts. If this is not the case, and the new bone which should contain salts is free from these constituents, soft lime-free bone is formed, and this gradually bends with the weight of the body and the child becomes rickety. In children the apposition of lime salts must be more rapid than the destruction. Metabolism is likewise going on in later life, and if the apposition of lime-containing bone does not keep pace with the destruction, the bones become poorer in lime salts, and, when this condition is extreme the bones bend, as in rickets, giving the picture of osteomalacia or, if the process is local, *osteitis deformans*. New bone is laid down but it is poor in calcium phosphate and richer in organic matter and magnesium phosphate. In old age, when the anabolic processes are retarded, a condition of increased metabolism of bone may not be followed by increased apposition of even lime-free bone and we may have the condition of osteoporosis known as senile osteomalacia. The difficulty which the aged have in supplying even lime-free bone is evident from the difficulty often seen in the production of a callus after a fracture. The histological appearance of the bone is of course different in these different conditions, but it is probable that so far as the bone itself is concerned the metabolic processes are similar. So far I have not referred to the cause of the disturbed bone metabolism but have merely described the process taking place. I shall next consider the cause of the disturbed bone metabolism in the case of osteomalacia.

### III THE ETIOLOGY OF OSTEOMALACIA

Osteomalacia has been attributed to bad hygienic conditions such as damp dwellings, lack of clothing, bad food, repeated pregnancies, protracted lactation, hard work, and care. It has been attributed to a

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38 Forster, J. Versuche über die Bedeutung der Aschenbestandtheile in der Nahrung, Ztschr. f. Biol., 1873, 11, 297

nitrifying ferment<sup>39</sup> Hoennicke<sup>40</sup> thinks that it is a disease of the thyroid gland, and Bossi<sup>41</sup> that it is a disease of the suprarenal capsules. The hypotheses most widely accepted, however, have been that the actual process is due to the action of an acid, commonly believed to be lactic acid, and that the condition is a disease of the ovaries. Let us first consider the acid theory.

### *1 The Action of an Acid in Causing Osteomalacia*

The hypothesis that osteomalacia is due to the action of an acid on the bones is based on the theory that in osteomalacia the process is one of halisteresis whereby the mineral constituents are dissolved and the organic matrix of the bone left behind. And this hypothesis falls with the fall of the halisteresis theory. Furthermore, recent investigations, which it will be unnecessary to go into in detail, have shown that the blood and tissue fluids do not become acid, that in the proportions of disodium hydrogen phosphate, monosodium hydrogen phosphate, sodium acid carbonate, and carbonic acid we have a delicate mechanism for preserving the neutral reaction of the blood and tissue fluids within very narrow limits. But, as the halisteresis theory had an apparent confirmation in the finding of lactic acid in the urine in osteomalacia, we must examine the evidence bearing on this point. Schmidt<sup>42</sup> states that he found lactic acid in the bones in osteomalacia, and Moers and Mück,<sup>43</sup> and Langendorff and Mommsen<sup>44</sup> state that they found this acid in the urine in cases of osteomalacia. These investigators boiled the ethereal extract of the urine with zinc oxid and, observing rhombic crystals in the dried residue, called them zinc lactate. A number of aromatic acids may go into solution in the ethereal extract whose zinc salts may be confounded with zinc lactate—hippuric acid, for example. In fact, by the same method, Langendorff and Mommsen found lactic acid in normal urine. Neither Schmuziger<sup>44</sup> nor Heuss<sup>45</sup> were able to find any lactic acid in

39 Petrone Osteomalakie, Centralbl f Gynak 1893, xvii, 392

40 Hoennicke, E Zur Theorie der Osteomalacie, zugleich zur Lehre von den Krankheiten der Schilddruse, Berl klin Wehnschr, 1904, xl, 1154, Ein Kaninchen mit experimenteller puerperaler Osteomalacie, Deutsch med Wehnschr, 1906, xxxi, 167

41 Bossi, L Nebennieren und Osteomalacie, Centralbl f Gynak, 1907, xxxi, 69, 172

42 Schmidt, C Knochenerweichung durch Milchsaurebildung, Ann d Chem u Pharm (Liebig's), 1847, lxI, 329

43 Langendorff and Mommsen Virchow's Arch f path Anat, 1867, lxix, 452

44 Schmuziger, F Zur Untersuchung bei puerperaler Osteomalacie, Centralbl f d med Wissensch, 1875, xiii, 946

45 Heuss, E Ueber das Vorkommen von Milchsaure im menschlichen Harne, Diss Leipsic, 1889

the urine in then cases, and in our case we looked for this substance in vain. There is, then, no good evidence that lactic acid occurs in the urine in osteomalacia.

Lactic acid has been fed to animals in the attempt to produce osteomalacia artificially. Thus Siedamgrotsky and Hofmeister<sup>46</sup> fed this substance in large amounts to goats and state that, as a result, the bones became poorer in lime salts. But Heiss<sup>47</sup> who fed from 2 to 8 gm. of lactic acid a day to dogs for nearly a year was unable to find that it had any effect whatever on the macroscopic or microscopic appearance or the chemical composition of the bones. It is not unlikely that, if there were any change in the bones in the experiment of Siedamgrotsky and Hofmeister, the most probable explanation is that it was due to digestive disturbances following the large amounts of lactic acid fed, for they obtained no such results after hydrochloric acid or sulphuric acid. So these experiments show negative results. Indeed, it takes concentrated lactic acid to decalcify bone *in vitro*, and it was such acid that Moers and Mück<sup>48</sup> and Henning<sup>49</sup> used to show that lactic acid will decalcify bone. Yet no one can suppose that concentrated lactic acid appears in the tissues. According to von Mosetig-Moorhof<sup>50</sup> even faintly concentrated lactic acid does not decalcify bone. Here again the results are negative.

The acidity of the blood has been determined by titration to find if there was decreased alkalinity in this disease. Renzi<sup>51</sup> von Jaksch,<sup>52</sup> Issmer,<sup>53</sup> Truzzi,<sup>54</sup> and Eisenhardt,<sup>55</sup> found decreased alkalinity. But

46 Siedamgrotsky and Hofmeister Die Einwirkung andauernder Milchsäureverabreichung auf die Knochen der Pflanzenfresser, Arch f Thierheilk, 1879, v, 243

47 Heiss, E Kann man durch Einführung von Milchsäure in den Darm eines Thieres dem Knochen anorganische Bestandtheile entziehen? Ztschr f Biol, 1876, xii, 151

48 Henning, C Die höheren Grade der weiblichen Osteomalacie, Arch f Gynak, 1873, v, 494

49 Von Mosetig Moorhof Milchsäure als Zerstörungsmittel pathogener Gewebe, Centralbl f Chir, 1885 xii, 193

50 Renzi, E de Chemische Reaction des Blutes, Virchow's Arch f path Anat, 1885, en, 218

51 Jaksch, R von Ueber die Alkaloesenz des Blutes bei Krankheiten, Ztschr f klin Med, 1887, viii, 350

52 Issmer, E Ueber die Zeitspanne der Menschlichen Schwangerschaft, Arch f Gynak, 1889, xxxx, 310

53 Truzzi Weiteres über die moderne chirurgische Behandlung der Osteomalacie und über das Wesen dieser Erkrankung, Centralbl f Gynak, 1892, vii, 574, Ancora sui risultati della moderna terapia chirurgica in casi di osteomalacia e sull' indole di tale affezione morbosa, Ann di ostet, 1891, viii, 601

54 Eisenhart, II Beiträge zur Aetiologie der puerpalen Osteomalacie, Deutsch Arch f klin Med, 1892, xlvi, 156

Truzzi found that this apparent decreased alkalinity persisted even after his patient was cured Fehling,<sup>55</sup> and von Limbeck<sup>56</sup> found no decreased alkalinity, and Senator<sup>57</sup> found the alkalinity increased It may be remarked that even a decrease in the alkalinity of the blood or tissue fluids would not make them a better solvent for calcium phosphate The actual presence of free acid is necessary and formation of acid in the tissues would not be shown by blood analysis, for such an acid would be immediately neutralized, just as the carbonic, sulphuric, and other acids constantly forming are continuously being neutralized And furthermore, we know now that we cannot determine the alkalinity of the blood by titration methods Beck<sup>58</sup> has made determinations of the nitrogen distribution in the urine in osteomalacia and, from his low figures for the amount of ammonia, we must conclude that there is no evidence of acidosis in osteomalacia Furthermore, in conditions of acidosis, for example in severe diabetic coma, there is no evidence of osteomalacia From beginning to end, the evidence in regard to the theory that the process in osteomalacia is due to the action of an acid is uniformly negative

## *2 The Relation of the Ovaries to Osteomalacia The Etiology of Puerperal Osteomalacia*

A consideration of the relation of the ovaries to osteomalacia brings up the whole question of the effect of the ovaries on the metabolism, the internal secretion of the ovaries and the effect of castration A study of the known data concerning this subject shows that very little accurate scientific work has been done The statements concerning the matter are mostly based on data that has to be excluded when critically examined, so that I felt obliged to take up the subject experimentally The results of that work, with the literature on the whole subject of castration, have just been published,<sup>59</sup> so that it will be necessary to give here only the chief conclusions together with a discussion of the bearing on osteomalacia

55 Fehling, H Ueber Wesen und Behandlung der puerperalen Osteomalacie, Arch f Gynak, 1891, xxxix, 171

56 Limbeck, R von Zur Kenntniss der Osteomalacie, Wien med Wchnschr, 1894, liv, 737, 793, 844

57 Senator, H Zur Kenntniss der Osteomalacie und der Organtherapie, Berlin klin Wchnschr, 1897, xxxiv, 109

58 Beck, M Ueber die gegenseitige Verhaltnisse der stickstoffhaltigen Substanzen im Harne bei Osteomalacie, Prag med Wchnschr, 1894, xix, 533

59 McCrudden, F H The Effect of Castration on the Metabolism, Jour Biol Chem, 1910, vii, 189

Let us consider first why osteomalacia has been believed to be a disease of the ovaries. At Poiré's suggestion, Fochier of Lyon<sup>61</sup> and Levy of Copenhagen,<sup>62</sup> among others, had carried out supravaginal amputation of the pregnant uterus and ovaries as a complement to Cesarean section in certain cases of osteomalacia and noted that the operation had a good therapeutic effect on the disease. As a result, Fochier proposed that this operation be tried in other cases of osteomalacia. Noting these results, and believing that the good effect might be due to the removal of the ovaries, Fehling<sup>63</sup> performed ovariotomy on a number of patients with osteomalacia and the operation was followed by good therapeutic results. He then expressed the opinion that osteomalacia was due to pathologically increased activity of the ovaries leading to stimulation of the vasodilators or paralysis of the vasoconstructors, followed by congestion and hyperemia of the bones and solution of the lime salts. In the light of results concerning the process in osteomalacia, I am inclined to suggest at once that there is no reason to believe that hyperemia of the bones would lead to increased catabolism of calcium rather than an increased anabolism. In other words, an increased blood-supply would lead only to increased metabolism as a whole, and there would be no loss of calcium. We need not concern ourselves, however, with the question of these details but only with the larger question as to whether or not osteomalacia is a disease of the ovaries. From the writings of travelers, and as a result of bairn raid and cattle-breeding experience, the sexual glands have long been supposed to have some control of the metabolism, especially over growth, and over the growth of the bones in particular.<sup>64</sup> Since Fehling first suggested castration as a therapeutic measure in cases of osteomalacia others have reported good results following this operation and the belief that osteomalacia is a disease of the ovaries has become quite general.

Let us consider first the effect of castration on the metabolism of normal individuals. This matter is discussed in detail in my paper already referred to, and the conclusion I was obliged to come to was that a careful study of very abundant clinical data in the case of human beings shows that castration has no effect on the general metabolism. I

<sup>61</sup> Levy Kaiserschnitt nach Poiré, Copenhagen, 1880. Quoted from Desiderius von Veltis Ueber die Heilung der Osteomalacie Im Anschluss an zwei durch Castration geheilten Fälle, *Ztschr f Geburtsh u Gynak*, 1892, xxviii, 323

<sup>62</sup> Fehling, II Ueber Wesen und Behandlung der puerpalen Osteomalacie, *Arch f Gynak*, 1891, xxiv, 171, Weitere Beiträge zur Lehre von der Osteomalacie, *Arch f Gynak*, 1895, xxviii, 472, Ueber Osteomalacie, *Ztschr f Geburtsh u Gynak*, 1894, xxii, 471

<sup>63</sup> This whole matter is discussed in detail in my paper already referred to (*Jour Biol Chem*, 1910, vii, No 3)

castrated several adult male and female dogs and made complete metabolism studies of the nitrogen, sulphur, calcium, magnesia and phosphorus for long periods, and was obliged to conclude that castration has no effect on the metabolism of adult animals. Less complete metabolism experiments on puppies have given likewise negative results. Comparative studies of the total amount of phosphate in normal and castrated animals have given negative results.

Comparative studies of the fat metabolism, of the storage of fat, and of the amount of oxygen used in cases of normal and castrated animals give similarly negative results. The feeding of ovaries and ovarian extracts have likewise led to negative results. Practically the only experimenters who find that castration has any effect on the metabolism are those whose experiments have been incomplete—who have studied the urine only. The experience of farmers, who find that by castrating male chickens they get a fatter bird, must be explained by the less active life of the capon compared with that of the active, aggressive cock. Excluding the results obtained in osteomalacia for the present, we see that experiments concerning the relation of the ovaries to the metabolism have given negative results. So far as I am able to find, castration has no effect on the metabolism. Let us next examine the results obtained by castration in osteomalacia.

It was a consideration of the results of my own experiments concerning the effect of castration on the metabolism that led to my conclusions concerning the etiology of the disease. If we take up these results first the results of other investigators will be clearer. In my first experiment I found, as already stated, a loss of calcium and phosphorus and a retention of magnesium, sulphur and nitrogen. After the first experiment the ovaries of the patient were removed and, a few months later, a second metabolism experiment of fourteen days' duration was carried out<sup>64</sup>. The condition of the patient improved as a result of the operation. Even union of a fractured bone took place. The second metabolism experiment showed retention of calcium as though the process had become cured. Table 15 shows the results<sup>65</sup> of the calcium metabolism.

64 Goldthwait, Painter, Osgood and McCrudden Am Jour Physiol, 1905, xiv, 211

65 Such a change for the better in the calcium metabolism in patients who were recovering was observed in a case studied by S Neumann (Weitere Untersuchungen über die Stoffwechselverhältnisse des Calciums, Magnesiums, der Phosphorsäure und des Nitrogens bei puerperaler Osteomalacie, mit besonderer Rücksicht auf die durch Castration und andere therapeutische Eingriffe verursachten Veränderungen des Stoffwechsels, Arch f Gynak, 1896, li, 130, also Quantitative

TABLE 15—METABOLISM OF CALCIUM OXID

In urine	5 40
In feces	1 80
<hr/>	
Total excreted	7 20
<hr/>	
In food	10 03
<hr/>	
Retention	2 83

The results so far appeared to confirm the opinion that osteomalacia is a disease of the ovaries. I then waited for over a year and then, on hunting up the patient to make a third metabolism experiment, found that her condition was worse than ever. About this time she had two slight fractures. Another metabolism experiment of six days was carried out and it was found that calcium was being rapidly lost again.<sup>2</sup> Table 16 shows the calcium balance. Castration did not cure the patient. There was apparently a temporary cure after the operation and then the pathological process started afresh later. Yet, if osteomalacia is due to a condition of overactivity of the ovaries, the conclusion seemed inevitable that the patient without ovaries could not have osteomalacia, and especially could not have such a process start afresh once it was stopped. This result led me to look up carefully the effect of castration in other cases of osteomalacia to see if the operation always resulted in a permanent cure.

TABLE 16—CALCIUM BALANCE

In urine	1 58
In feces	6 69
<hr/>	
Total excreted	8 27
<hr/>	
In food	3 44
<hr/>	
Loss	4 83

An examination of the clinical results of castration in osteomalacia naturally began with an examination of the cases of Fehling. By 1895 Fehling had reported fourteen cases of osteomalacia treated by castration.<sup>66</sup> Of the patients but six were well three years after the operation. Two were not cured, and one of these, as in my own case, showed a temporary improvement and then became worse. The others either died

Bestimmung des Calciums, Magnesiums, und der Phosphorsäure im Harn und Kot bei Osteomalacie, Arch f Gynak, 1894, xlvi, 202), and by G. Hotz (Phosphorsäure und Kalkstoffwechsel bei Osteomalacie unter Einfluss der Phosphortherapie, Ztschr f exper Path u Therap, 1906, iii, 605).

<sup>66</sup> Fehling, H. Weitere Beiträge zur Lehre von der Osteomalacie, Arch f Gynak, 1895, xlvi, 472.

or were lost track of Von Winckel<sup>67</sup> reported three cases, of which one was improved after castration Wheaton<sup>68</sup> tried castration in one case without benefit Polgár<sup>69</sup> tried the operation in six cases A cure followed in but two Latyko<sup>70</sup> castrated one patient, but without effect In one out of two cases Neumann<sup>65</sup> failed to help by castration Truzzi<sup>72</sup> reported 97 cases of osteomalacia treated by castration, 16.9 per cent of the patients were not cured These results have not been especially selected to show that castration is not always followed by cure, but include most of the results reported in the literature Yet a very large percentage of patients were not cured by the operation Furthermore, most of them were not followed for any length of time so that the percentage of cures is probably much less even than the figures indicate, for, in the cases that were followed, mine and Fehling's, some of the apparent cures were found to be only temporary If osteomalacia is due to overactivity of the ovaries, it is difficult to understand how a patient without ovaries can have osteomalacia It might be suggested that perhaps the process, once started by overactivity of the ovaries, keeps on for some reason even after these organs are removed, but opposed to this view we have the cases of patients who were temporarily cured by castration and in whom the process started again later I shall return later to the causes of the good effect of castration in osteomalacia, but the point to be made here is that in a large percentage of cases, castration does not cure osteomalacia This finding leaves us with no evidence in favor of the hypothesis that osteomalacia is a disease of the ovaries

As opposed to the view that osteomalacia is a disease of the ovaries, we have besides the negative results of castration on many cases of the disease, the negative findings in histological examination of the ovaries in these cases A number of such ovaries have been investigated Bulius<sup>73</sup> made a careful study of six cases and found no change He was obliged to criticize an earlier paper of his own, in which he found a certain amount of hyperemia and hyalin degeneration of the arterial walls In this connection, we think, too, of the cases of osteomalacia in young women before the ovaries have begun to function and especially of the cases

67 Winckel, F von Ueber die Erfolge der Castration bei ber Osteomalacie, Samml klin Vortr (Volkmann's), new series, No 71

68 Wheaton, C Osteomalacia, Northwest Lancet, 1891, xi, 389

69 Polgár, E Die Heilung der Osteomalacie mittelst Castration, Arch f Gynak, 1895, xlvi, 30

70 Latyko, W Ueber Osteomalacie, Allg Wien med Ztg, 1893, xxxviii, 393, 403

72 Truzzi Ann di ostet, 1894, cited by Fehling, Arch f Gynak, xlvi, 472

73 Bulius, G Osteomalacie und Eierstock, Beitr z Geburtsh u Gynak, 1898, 1, 138

of osteomalacia in men. Such cases are rare, but they do occur and autopsy has confirmed the diagnosis in some cases. If, then, osteomalacia is not a disease of the ovaries, what is the cause, and how do we explain the good effects of castration?

If we bear in mind the facts already pointed out, that the bones are constantly undergoing metabolism, we see one direction in which to look for the cause of osteomalacia. When the necessity of the organic food material is increased without a corresponding increase in the supply, or when the supply is decreased, as in starvation, the glycogen and fat stored in various parts of the body are gradually transferred to parts of the body where needed and there used up. If now, in some way, the need for lime salts is suddenly greatly increased, the catabolism of bony tissue must be increased. And since, except in rare cases, osteomalacia occurs only in pregnancy, we immediately think of the growing fetus with its large demand for calcium for its bony tissue as the cause of the increased catabolism of the bones of the mother. This possibility indicates the direction in which to look for evidence.

A strong point in favor of this opinion that the growing fetus causes a certain drain on the lime salts in the mother's bone is to be found in the observations of Hanau.<sup>23</sup> This investigator found at autopsy changes similar to osteomalacia in the bones, and especially the bones of the pelvis, of twenty women who were apparently free from any symptoms of this disease during life. A clinical observation of Fehling's<sup>15</sup> fits in with these findings. Fehling has observed that many women who have several quickly succeeding pregnancies have pain and tenderness in the pelvic bones as in osteomalacia but without deformity, and has suggested that these are lighter grades of osteomalacia. It seems probable, then, that in pregnant women, the normal catabolic processes in the bones are increased just as the normal catabolic processes in general are increased on behalf of the fetus and that, in osteomalacia, we are dealing with extreme cases of a normal process.

Clinical evidence, too, points in this direction. Careful examination of the clinical histories of as many cases of osteomalacia as could be found in the literature brought out certain facts that had not before been emphasized. In the first place, osteomalacia rarely begins in the first or even in the second pregnancy but usually only after several rapidly succeeding pregnancies, and, furthermore, is usually seen in poor women whose hygienic environment is bad. As a rule, the first attack appears in the later months of pregnancy and the patient usually recovers after parturition. A second attack may not occur. But, if pregnancies succeed each other rapidly, other attacks occur, and the succeeding attacks begin earlier

and earlier in succeeding pregnancies, are more severe, and last longer after the pregnancy is ended, until finally there is no recovery. In other words, it is only after a long-continued and severe drain on the bones of a poorly nourished patient that the body fails to respond to the demands on it, and even then recovery follows if the severe demands are not continued. Of course not every case runs like this, but this is the typical course of the disease.

These clinical features seemed so important and suggestive that a search was made especially to see if other investigators had not made any similar observations. It was found that Cohnheim<sup>76</sup> mentions the fact that it is common for osteomalacia to heal after the first pregnancy and then undergo an exacerbation during each succeeding pregnancy. Latyko,<sup>70</sup> too, has made observations nearly similar to mine regarding the clinical course of the disease. The observation made by Cohnheim<sup>76</sup> that fractures occurring during pregnancy are slowly repaired because a proper callus is formed with difficulty, is a point in favor of my theory. In the case of the fracture, there is a lack of lime salts for the formation of new bony substance. In the case of osteomalacia, there is a lack of lime salts for the formation of normal bone to take the place of that which is being destroyed, at an increased rate on account of the pregnant state. Both histological and clinical evidence, then, are in favor of the view that osteomalacia is but an exaggeration of the increased metabolism of the bony tissues in pregnancy, and the question naturally comes up as to whether there is any chemical evidence pointing in the same direction.

As chemical evidence in this direction we must consider the metabolism experiment of Neumann<sup>65</sup> on a patient with osteomalacia during pregnancy. Instead of a loss of calcium, he found a retention in this case (Table 17). There was likewise a retention of magnesium and phosphorus. These are the only elements he studied. Here the abnormal process is going on and magnesium is retained. The calcium phosphate is not excreted but given up to the fetus. That a healthy fetus can develop in a woman who has osteomalacia and who therefore is not in a condition to give up lime salts without severe consequences to her own tissue is not surprising in view of the results of Jageroos,<sup>77</sup> who showed in experiments on dogs that a fetus can develop at the expense of the mother even when there is a negative phosphorus, nitrogen, and salt balance in the metabolism of the mother.

76 Cohnheim, J. Lectures on General Pathology Eng transl by A McKee, 1889, vol 11, sect 2, p 636

77 Jageroos, B. Studien über den Eiweiss, Phosphor, und Salzumsatz während des Gravidität, Arch f Gynak., 1902, lxxvii, 517

That is to say, when there is not enough material in the food even for the mother alone, the fetus continues to grow and the growth here, as in osteomalacia, is at the expense of the tissues of a mother who is not in condition to give up material. The chemical evidence, then, is not abundant but is in accord with our view concerning the etiology of the disease.

TABLE 17.—CALCIUM OXID AND PHOSPHORUS PENTOXID IN OSTEOMALACIA DURING PREGNANCY

	CaO	MgO	P <sub>2</sub> O <sub>5</sub>
In food	12.10	2.01	14.70
In excreta	9.97	1.72	13.26
Retained	2.13	0.28	1.44

The question then comes up as to why castration cures in some of the less severe cases of osteomalacia. The answer is simple. A great many different kinds of treatment besides castration have been followed by either temporary or permanent cure in cases of osteomalacia. Thus, chloral<sup>78</sup> sulphur baths<sup>79, 80</sup> chloroform narcosis,<sup>76</sup> and especially phosphorus<sup>80</sup> have cured many cases. The cures following injection of adrenalin have even led Bossi<sup>81</sup> to the conclusion that osteomalacia is a disease of the supraenal glands. Good hygienic treatment alone is very effective,<sup>82</sup> and, furthermore, many patients recover without any treatment. On the other hand all these measures, including castration, sometimes fail. Besides our case, only one other case of non-puerperal osteomalacia can be found in the literature in which castration was tried.<sup>83</sup> The operation in our case failed to cure the patient. In the other case the patient was said to be improved after three months but was not further followed. The important thing to note in the case of the castration therapy is that it prevents further pregnancies so that, except in severe cases, the cure is likely to be permanent.

So far then as puerperal osteomalacia is concerned, we can say that it is not a disease of the ovaries, but an exaggeration of a process that is

78 Petrone Osteomalacie, Centralbl f Gynak, 1893, viii, 392

79 Weisz, E Beitrag zur Heilung der Osteomalacie, Wien klin Wehnschr, 1894, vii, 423

80 Sternberg, M Ueber Diagnose und Therapie der Osteomalacie, Ztschr f. klin Med, 1893, xxii, 265 Hoxter, O Beiträge zur quantitativen Harnanalyse bei Osteomalacie unter dem Einfluss der Phosphortherapie, Ztschr f exper Path u Therap, 1906, iii, 605 Siegeit, F Ueber typische Osteomalacie im Kindesalter, Munchen med Wehnschr, 1898, xl, 1401 Beinstein Die Oophorinbehandlung bei Osteomalacie, Munchen med Wehnschr, 1898, xl, 427

82 This probably explains the temporary improvement of our patient

83 Hofmeier, M Zur Frage der Behandlung der Osteomalacie durch Castration, Centralbl f Gynak, 1891, v, 225

normally going on. Normally the anabolic and catabolic processes in the bones balance each other. In pregnancy, as a result of increased needs of the fetus for lime salts, the apposition of lime salts in the bones may not quite make up for the lime salts destroyed and the new bone formation contains less lime. If this latter process is greatly exaggerated, the bones can not preserve their rigidity and the patient has osteomalacia.

### 3 Non-puerperal Osteomalacia

If puerperal osteomalacia is, then, due to a disturbance of the equilibrium of the calcium phosphate metabolism, we might expect that other conditions might occasionally lead to a condition similar to that seen in puerperal osteomalacia either by decreased calcium anabolism or by increased calcium catabolism. As a matter of fact, we do find cases of non-puerperal osteomalacia. The disease has occasionally been reported in men and in unmarried women. The patient whose metabolism we studied was an unmarried girl 18 years old. One of the bones which we analyzed came from a young man with the disease. Among 360 cases of osteomalacia reported by five writers, there were 39 cases of the disease in men, but, as these statistics are old, there is some question about the diagnoses. Without making a special search for all cases, I was able to find ten cases of the disease reported in unmarried women during the last twenty-five years—the diagnosis being confirmed in some cases by autopsy—and nine cases in men, four of which were confirmed by autopsy. Concerning the cause in these cases we know little, probably because a systematic search has not been made for a cause. Calcification of various tissues is not at all uncommon and a number of papers have been appearing lately showing that heteroplastic bone formation is not very rare. In a recent paper on the subject Buerger and Oppenheim<sup>84</sup> point out that such bone formation has been found in the dura, pia, choroid, muscles, bladder, scars, lungs, pleura, eye, stomach, liver, and lymph-nodes. Systematic search might show in these cases what Hanau's investigation showed in pregnant women, that a certain degree of decalcification of bones frequently takes place to supply the lime needed even though it is not great enough to give symptoms of osteomalacia. And, on the other hand, careful search at post-mortem examination might show where the lime salts were going to in these non-puerperal cases. Henning<sup>48</sup> refers to the abundance of concretions of lime salts in different parts of the body, especially the kidneys.

84 Buerger, L., and Oppenheim, A. Bone Formation in Sclerotic Arteries, Jour Exper Med., 1908, x, 334.

in osteomalacia but does not give enough data. Beiger<sup>86</sup> also refers to these kidney and bladder-stones. This author refers also to two cases of osteomalacia following osteotomy and states that the disease often follows an accident, he questions if the afflux of lime salts for repair of the wound may not be the start of a process of decalcification of other parts which prolongs itself even after the need has stopped. He states that the calcium excretion in one of these cases was 90 gm. of calcium oxide per day—an enormous amount. This suggestion of a production of an excess of lime salts after the need for them has ceased is a good one. It is not uncommon for the body to continue a process once started even after the need for it has ceased. The production of certain antitoxins is an example of this. An example of this is also seen in the metabolism experiment on my patient. When she began to improve after the operation, and calcium was retained, the retention of sulphur did not cease at once but only later. Another observation in this line is that of Kehler that when healing of the bones does take place in cases of osteomalacia they become especially hard. This matter will be referred to again later. We must conclude however, that, although we understand the process, the cause for these rare cases of non-puerperal osteomalacia is not always clear.

#### 4 Artificial Osteomalacia

If osteomalacia can be produced by a naturally occurring drain on the lime salts of the bones, it seems probable that a similar condition might be produced artificially. Chossat<sup>87</sup> was the first to try such an experiment. He fed pigeons a diet poor in lime salts. The bones became thin and fractured easily, and post-mortem examination showed that they were partly made up of soft cartilaginous material. Edwards<sup>88</sup> repeated the experiment and produced a condition more nearly like osteoporosis. In this case, the bone was destroyed as a whole, organic and inorganic material together but, apparently, no new bone was laid down. Roloff<sup>89</sup> produced rickets in young dogs and swine which were fed a diet poor in lime salts. Voit,<sup>90</sup> also, produced rickets in puppies fed on such a diet.

86 Beiger Amélioration spontanée survenue dans un cas d'osteomalacie masculine arrivé aux déformations les plus extrêmes avec complications de lithiasè vésicale et rénale, *Presse méd.*, 1905, viii, 249.

87 Chossat Note sur le système osseux, *Compt rend de l'Acad d sc.*, 1842, xiv, 451.

88 Edwards, A. Expériences sur la nutrition des os, *Compt rend de l'Acad d sc.*, 1861, lii, 1327.

89 Roloff, F. Ueber Osteomalacie und Rhachitis, *Arch f Thierheilk.*, 1875, i, 189.

90 Voit, E. Ueber die Bedeutung des Kalkes für den thierischen Organismus, *Ztschr f Biol.*, 1880, xvi, 55.

The experiments of Stilling and Mering<sup>91</sup> and Roloff<sup>92</sup> are conclusive regarding the production of puerperal osteomalacia. Stilling and Mering fed a female dog on a diet poor in calcium salts during the whole of the period of pregnancy. After parturition, the dog was killed and was found to have true osteomalacia in the bones of the pelvis and ribs. Roloff performed a similar experiment on a sheep and continued the diet poor in calcium throughout the period of lactation. The sheep became lame and showed the clinical picture of osteomalacia. Post-mortem examination showed a condition of true osteomalacia in the bones. It is not to be supposed that it is a diet poor in calcium that brings about the condition in human beings, but the feeding of such a diet to pregnant animals gives the best conditions for the artificial production of the disease. These experiments are in complete accord with my views regarding the etiology of osteomalacia.

### *5 The Replacement of Calcium by Magnesium in Osteomalacia*

One more point that is best treated at this place is the question of the partial replacement of calcium by magnesium in these cases. I am not dealing here with ion action, so that the quite opposite physiological effect of these elements does not come into consideration. The calcium phosphate is used to make the bony structure rigid, and a partial substitution in a time of need by the similarly insoluble magnesium phosphate does not seem out of the question. There is, too, experimental evidence that calcium can be replaced in part by similar elements under certain conditions. Thus König<sup>93</sup> fed three sets of young rabbits food poor in calcium phosphate. To the diet of one set, calcium phosphate was then added, to the diet of another set, magnesium phosphate, and to the diet of the third set, strontium phosphate. The rabbits which were given magnesium phosphate were found to have twice as great an absolute amount of magnesium in the bones as the others. In the case of the rabbits fed strontium phosphate, an element foreign to the body, the amount of calcium in the bones was decidedly decreased and about 5 per cent strontium found instead. The earlier experiments of Weiske<sup>94</sup> when he used adult animals gave

91 Stilling, H., and Mering, J. Ueber experimentelle Erzeugung der Osteomalacie, Centralbl f d med Wissensch, 1889, xxvii, 303

92 Roloff Ueber Osteomalacie und Rhachitis, Arch f Thierheilk, 1879, v, 152

93 König, J. Substitution des Kalkes in den Knochen, Ztschr f Biol, 1874, x, 69

94 Weiske, H. Ueber den Einfluss verschiedenen der Nahrung beigemengte Erdphosphate auf die Zusammensetzung der Knochen, Ztschr f Biol, 1892, viii, 239

negative results, but later experiments,<sup>95</sup> in which he used young animals, gave results like those of König. It is clear, then, that magnesium can act as a substitute for calcium in the bones when the organism has not enough calcium at its disposal.

#### IV THE METABOLISM IN DIFFERENT STAGES OF THE DISEASE

A closer examination of the results of the metabolism experiments in different stages of the disease gives a clearer picture of the process going on. Tables 18, 19, and 20 give a summary of the results of three of our metabolism experiments during the different stages of the disease.

TABLE 18—METABOLISM DURING THE ACTIVE STAGE OF OSTEOMALACIA

S days	CaO	MgO	P <sub>2</sub> O <sub>5</sub>	S	N
Total excreted	5.66	2.015	12.37	2.68	63.02
In food	4.56	2.207	12.05	7.15	69.12
Retention	—1.10	+0.192	—0.32	+4.47	+6.10

The experiment<sup>64</sup> shown in Table 18 was carried out during the active stage of the disease. There was a loss of calcium and phosphate and a retention of sulphur and magnesium.

TABLE 19—METABOLISM AFTER REMOVAL OF OVARIOS

14 days	CaO	S	N
Total excreted	7.20	4.84	101.3
In food	10.03	10.54	127.0
Retained	+2.83	+5.70	+22.7

The experiment<sup>64</sup> shown in Table 19 was performed after the ovaries were removed and as soon as the patient began to show signs of improvement. Magnesium and phosphate were not studied. The improvement had led to retention of calcium. There was also a retention of sulphur, probably because the improvement had only just begun. The retention of sulphur persisted for a time and did not become normal as soon as the improvement in the calcium metabolism appeared. The retention of sulphur was not so great as in the first experiment, however. In the first experiment the ratio of the sulphur retained to that of the nitrogen was 73:100. In this experiment it was only 25·100. In all probability the good hygienic conditions in the hospital were as much responsible for the temporary improvement in this case as the operation. The retention of

95 Weiske, H. Versuche über die Wirkung einer Beigabe von Calcium, Strontium, resp. Magnesium carbonat zu einem kalkarm, aber phosphorsaurereichen Futter auf den thierischen Organismus insbesondere auf die Zusammensetzung des Skelettes, Ztschr f Biol., 1895, xxxi, 421.

so much nitrogen is in accord with this belief. The patient continued to improve for some time after this and there was union of a bone on which osteotomy had been performed.

TABLE 20.—METABOLISM A YEAR AFTER TABLE 19

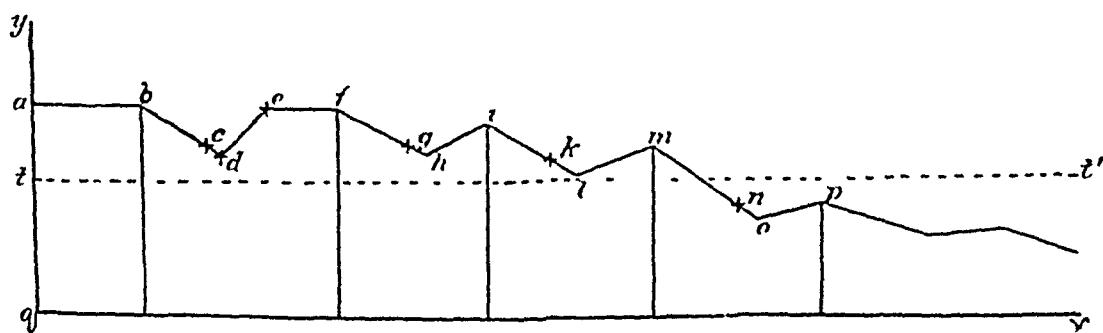
6 days	CaO	MgO	P <sub>2</sub> O <sub>5</sub>	S	N
Total excretion	8 27	1 764	10 35	2 793	34 68
In food	3 44	1 504	12 28	2 897	38 85
Retained	—4 83	—0 260	+1 93	+0 104	+4 17

The experiment<sup>2</sup> shown in Table 20 was performed more than a year after the second experiment. Just before this experiment the condition had begun to grow worse. Two spontaneous fractures had occurred a few weeks previously. In this experiment, again, there was a loss of calcium, which, judging from the clinical condition, had begun recently. The sulphur metabolism nearly balanced. A marked retention had hardly begun. This is a condition which might well explain the occurrence of the fracture. There was an increased catabolism of the bone to which the body had not yet responded by an increased apposition, a condition leading to a temporary osteoporosis. In both the second and the third experiment it will be seen that an increased catabolism or anabolism of bone is not immediately followed by an increase in the reverse process. The slow response to changed conditions in the metabolism is seen, too, in the later and later recovery from attacks of osteomalacia after successive pregnancies until finally there is no recovery and the increased calcium catabolism continues. This, too, is quite in accord with the hypothesis that some of the cases of non-puerperal osteomalacia may have been due primarily to a need for calcium by other parts of the body and that the increased catabolism so started becomes permanent. The cases of osteomalacia in males, already spoken of, which were apparently started by a need of calcium to repair broken bones are in accord with this hypothesis.

The retention of calcium during an improvement in the condition is also shown in other experiments. The metabolism in osteomalacia during pregnancy has been spoken of already. In this case, as we should expect, there is retention of calcium even during the active stage of the disease. But this retention is probably only an apparent one since the calcium goes to the fetus and is not retained by the mother herself. Finally, in the very last stages, after the amount of calcium phosphate in the bones has decreased to a very low level, the body is able to maintain a calcium balance at this low level for a time before death.

## V. SUMMARY OF THE ETIOLOGY AND THE COURSE OF THE DISEASE

Putting our results together, we get a picture of the course of the disease. A need of calcium phosphate by the growing fetus is responded to by an increased catabolism of the bones of the mother. This may be balanced by an increased apposition of the normal bone or, in a poorly nourished woman of low vitality, by apposition of bone poorer in lime from lime but containing a slightly increased amount of magnesium phosphate. After the end of gestation, or lactation, when the need for calcium phosphate has ceased an apposition of normal bone may begin and the patient may recover. After repeated, rapidly following pregnancies, the amount of calcium phosphate in the bones becomes less and less. A new pregnancy begins before the organism has made up for the loss of calcium phosphate in the preceding pregnancy. And further the long-continued increased catabolism continues longer after the need for it has ceased. Finally, the decrease in the calcium phosphate of the bones is so great that it is beyond the power of the patient to increase the anabolic processes to such an extent that they will not only balance the increased catabolism but that earlier losses will be made up. In the very last stages, the body has lost so much calcium that the total amount in the bones is very low, the daily loss becomes very small, and a balance can be maintained on this very low level for a time before death.



We might even represent a typical case by such a figure as the accompanying illustration.

The line  $qr$  represents time,  $qy$  the amount of calcium phosphate in the bony system. The perpendicular lines represent the beginning of pregnancies,  $qa$  is the normal amount of calcium phosphate,  $qt$  is the amount below which symptoms of osteomalacia appear. At  $b$ , we may imagine a pregnancy to begin, and at  $c$  lactation is supposed to end. Recovery begins soon after, at  $d$ , and is complete at  $e$ . Another pregnancy begins at  $f$ . Recovery begins at  $h$  and a new pregnancy at  $i$  before recovery is complete. Recovery after the next pregnancy at  $m$  is less complete and, finally, in the next pregnancy symptoms of osteomalacia appear and the disease becomes permanent. The periods  $cd$ ,  $gh$ ,  $il$ ,  $no$ ,

the lengths of time after parturition or lactation that recovery begins, become successively longer and longer. The lines *de*, *hi*, *lm*, *op*, become successively less steep, indicating more prolonged convalescence.

In cases of non-puerperal osteomalacia, it seems likely that some long-continued need for calcium, such as undoubtedly often occurs, starts an increased catabolism of the bones which in some cases may persist after the primary need has ceased.

In rickets, osteitis deformans, and senile osteomalacia, the process would seem to be similar although the course and histological appearance may be different. In young infants, a balanced metabolism of calcium phosphate is not sufficient. The apposition of new normal bone containing lime salts must be more rapid than the destruction and whatever interferes with this preponderance of anabolism over catabolism may lead to rickets. In senile osteomalacia, the condition is one of osteoporosis. The bones become not soft, but thin, owing to the fact that increased bone catabolism is not responded to in the aged by an apposition of even soft lime-free bone. In osteitis deformans, we have a condition of local osteomalacia.

#### VI THE TREATMENT OF OSTEOMALACIA

From what has been said concerning the etiology of osteomalacia, it will be seen that the treatment depends on the individual case. It is probably useless to resort to castration in a condition of non-puerperal osteomalacia or a very severe case of puerperal osteomalacia, and, in mild cases of puerperal osteomalacia, it is usually needless to resort to this operation. Good hygienic conditions should be relied on to improve a mild case and the patient should be advised concerning the dangers of rapidly occurring pregnancies. The recent results in bringing about artificial menopause by the  $\gamma$ -rays<sup>96</sup> leads me to suggest that this treatment might be tried instead of the more severe operation in a case in which sterilization seemed advisable.

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96 Halberstaedter, L. Die Einwirkung der Rontgenstrahlen auf Ovarien, Berl klin Wchnschr, 1905, xlii, 64 Cournelle, F de Action atrophique glandulaire des rayons de Rontgen, Semaine méd., 1905, xxv, 116, Stérilisation ovarique chez la femme par les rayons de Rontgen, Semaine méd., 1907, xxvii, 508

# THE SYMPTOM-COMPLEX OF THE ACUTE POSTERIOR POLIOMYELITIS OF THE GENICULATE, AUDITORY, GLOSSOPHARYNGEAL AND PNEUMOGAS- TRIC GANGLIA

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In previous communications<sup>1</sup> I have already elaborated in some detail the symptomatology and complications of the posterior poliomyleitis of the geniculate ganglion of the facial nerve, a syndrome which is characterized by herpes zoster oticus, facial palsy and auditory symptoms. When the ganglion alone is involved herpes oticus results, the eruption being distributed in the central portions of the external ear. If the inflammation extends from the ganglion to the nerve-trunk, facial palsy follows, and when deafness and symptoms of Ménière's disease occur they are produced either by an extension of the inflammatory process to the adjacent auditory nerve or by simultaneous involvement of the peripheral auditory ganglia (Fig. 1).

I shall now consider the localization of the same process in the peripheral root ganglia of the glossopharyngeal, vagus, and auditory nerves, their respective neural complications and the various clinical combinations which may occur.<sup>2</sup> I shall also endeavor to differentiate the zoster zones of the geniculate, glossopharyngeal, and vagal ganglia on the external ear, and within the buccal cavity. It may be said in general that all of these clinical types are related, and together form a definite group of cases, which is characterized by herpes zoster of the cephalic extremity, with facial palsy, auditory, and pneumogastric symptoms in various combinations.

This group forms an interesting chapter of herpes zoster, an affection which is distinguished by an eruption of herpetic vesicles, usually unilateral, and strictly limited to a definite area of the skin or mucous membrane (the zoster zone). The underlying lesion is an inflammation in

<sup>1</sup> Hunt, J Ramsay Herpetic Inflammation of the Geniculate Ganglion, a New Syndrome and Its Complications, *Jour Nerv and Ment Dis*, 1907, **xxiv**, 73, *id*, Otalgia Considered as an Affection of the Seventh Cranial Nerve, *Arch Otol*, 1907, **xxxvi**, 371, *id*, Ein Fall von Poliomyelitis posterior des Ganglion Geniculi, *Neurol Centralbl*, 1908, **vii**, 514.

<sup>2</sup> Hunt, J Ramsay The Paralytic Complications of Herpes Zoster of the Cephalic Extremity, a Preliminary Report on the Herpetic Inflammations of the Geniculate, Glossopharyngeal, Vagal and Acoustic Ganglia, *Jour Am Med Assn*, 1909, **lvi**, 1456.

the sensory ganglion or ganglia corresponding to the eruption. The eruption is usually confined to the distribution of a single ganglion, but this is not always so, and double, triple, and even multiple forms occur. The region of the head and neck is especially liable to involvement of more than one ganglion in zona.

In my previous papers, I have particularly emphasized the occasional presence of inflammatory reactions in those ganglia situated immediately

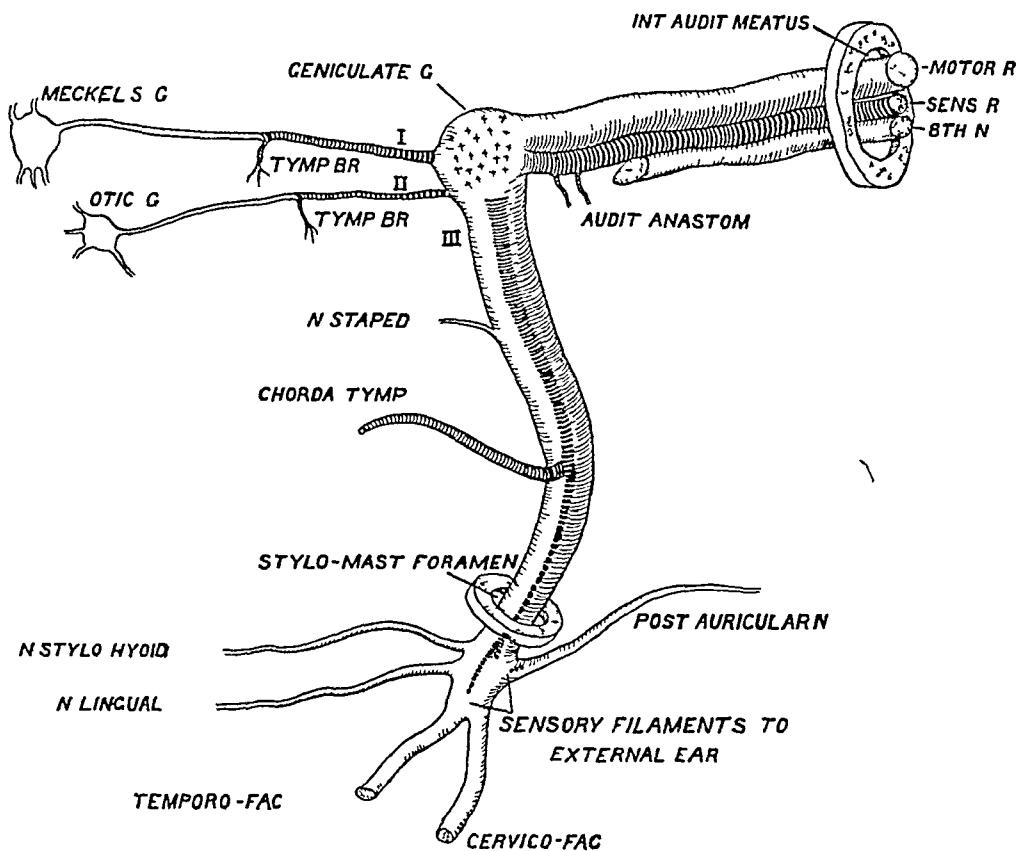


Fig. 1.—Diagrammatic representation of the facial nerve, showing its ganglion, motor and sensory roots, and peripheral divisions. Division I. The great superficial petrosal nerve passing to Meckel's ganglion, with its tympanic branch (great deep petrosal). Division II. The small superficial petrosal nerve passing to the otic ganglion, with its tympanic branch (small deep petrosal). Division III. Including the motor trunk, chorda tympani and sensory filaments for the external ear.

above or below the chief or eruptive focus, or that corresponding to the zoster zone. I would draw attention again to this serial involvement of ganglia as having an important bearing on the neural complications which are to be considered later.

The specific infective agent of zona is unknown, but whatever its nature may be, it possesses a definite and special affinity for certain ganglionic structures, of which the posterior root ganglia of spinal nerves

and the Gasserian ganglia are types. It produces in these structures an inflammation, having the same general pathological characteristics as the acute anterior poliomyelitis. Because of the similarity between these two inflammatory affections, one of the anterior horns, the other of the posterior ganglionic chain, herpes zoster has been termed an acute posterior poliomyelitis (Head and Campbell<sup>3</sup>).

It is now generally accepted by anatomists that the geniculate glossopharyngeal, pneumogastric, and even the acoustic ganglia, are homologues of the posterior spinal ganglia, and form an integral part of this ganglionic chain. For this reason, I believe that these ganglia may also be involved in the specific infection and inflammatory reactions of zona (posterior poliomyelitis). Recent investigations have shown that the acute anterior poliomyelitis occasionally invades the motor cranial nerve ganglia, the same is also true of posterior poliomyelitis and the various root ganglia of the seventh, eighth, ninth and tenth nerves, giving rise to a series of interesting syndromes, the real nature and significance of which have not been recognized.

The nerve complications which arise, like the herpetic eruption, are unilateral, and are produced by an extension of the inflammatory process in the ganglion to the adjacent fibers of the seventh, eighth, ninth and tenth nerves. These may occur with the outbreak of the eruption, or, as more commonly happens, several days, or even a fortnight later. This period of quiescence or latency intervening between the appearance of the eruption and that of the nerve involvement, suggests that the inflammatory process in the ganglion may be more or less progressive in character in its earlier stage and has not reached its full height with the appearance of the vesicles. This tendency to slight progression receives a further clinical corroboration from the occurrence of successive crops of vesicles in the earlier period of the disease.

The clinical statistics which are utilized in my paper are based on the records of eighty-seven cases of herpes zoster of the cephalic extremity, in which there was an associated facial palsy. In this entire series, the eruption was limited to one or more of the zoster zones of the head and neck. Among these cases there were many with auditory complications, and a few with symptoms pointing to involvement of the pneumogastric nerve. In order to illustrate the various clinical types, my own unpublished cases will be presented in abstract form, together with certain cases recorded by other observers illustrating special features of the disease.

The subject-matter will be considered under the following general headings:

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<sup>3</sup> Head, H., and Campbell Pathology of Herpes Zoster, *Brain*, 1900, xxiii, 353

- 1 Report of personal cases of herpes zoster oticus
- 2 The zoster zones of the geniculate, glossopharyngeal, and vagal ganglia on the external ear (herpes zoster oticus)
- 3 The paralytic complications of herpes zoster oticus
- 4 The intra-oral zoster zones of the glossopharyngeal, and vagal ganglia (herpes zoster pharyngis and herpes zoster laryngis)
- 5 The complications of herpes zoster pharyngis and herpes zoster laryngis
- 6 Herpes zoster of the tongue with facial palsy
- 7 Posterior poliomyelitis of the auditory ganglia
- 8 The paralytic complications of herpes zoster facialis and herpes zoster occipitocollaris
- 9 Concluding remarks

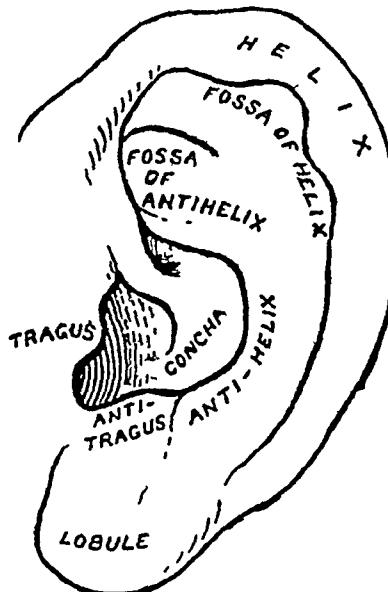


Fig 2.—The topographical landmarks of the external ear

#### *1 REPORT OF PERSONAL CASES OF HERPES OTICUS*

CASE 1—*Herpes Zoster Oticus*—(Neurological service of Prof Dana, Cornell Medical School) W F, aged 16, in good health Onset Nov 16, 1907, with headache, chilly sensations and pain in the occipital region. The patient was unable to work and remained at home several days, there was no vomiting but considerable nausea with fever. The patient was examined in the Cornell Medical Clinic, November 20. On admission his temperature was 102, pulse 108. There was an eruption of herpes in the left ear which had made its appearance on November 17. There was no discharge from the ear, and the hearing was not affected, there was no tinnitus aurium. The eruption had the following distribution. A small group on the posterior half of the concha, a somewhat larger group immediately posterior to this on the antihelix, another on the posterior portion of the antihelix and one just beneath its fold, in the postero superior boundary of the concha. The auricle was somewhat swollen. There was no eruption within the canal, no vesicles on the face or neck. The innervation of the facial nerve was equal on the

two sides Objective examination of the ear was negative There was some hypalgesia in the region of the eruption

CASE 2—*Herpes Zoster Oticus*—(Referred from the New York Eye and Ear Infirmary Service of Dr. Whiting) Mrs L, aged 22, in good health Onset Monday, Jan 4, 1909, with roaring in the right ear During the day there were severe pains in the auditory canal and mastoid region The next day, the lower half of the auricle became swollen, tender and bluish-red in color, and an eruption made its appearance in the swollen area A few enlarged tender glands were palpable below the auricle The tinnitus aurium continued for several days and the hearing was slightly reduced on the affected side The eruption had the following distribution the antitragus and the helix immediately above and the lobule immediately below the antitragus All trace of the vesicles disappeared in two weeks The canal and tympanum were free from vesicles, as were also the face and neck



Fig 3—Diagram of the sensory nerves of the scalp and face, (1) great occipital, (2) small occipital, (3) auricular branch of the pneumogastric, (4) great auricular, (5) auriculotemporal, (6) temporal branch of superior maxillary nerve, (7) supra-orbital, (8) supratrochlear, (9) malar branch of superior maxillary nerve, (10) infratrochlear, (11) nasolobular, (12) infra-orbital, (13) buccal branch of inferior maxillary nerve, (14) mental (From Holden's Anatomy )

CASE 3—*Herpes Zoster Oticus*—(Referred from the Otological Clinic of the Cornell Medical School by Dr McAuliffe) Miss F, aged 18, in good health Onset in August, 1908, with severe pains in the lobule of the left ear and in the depth of the auditory canal, of a sharp, shooting character On the third day there appeared several small groups of herpetic vesicles on the posterior mesial surface of the auricle and the adjacent mastoid region, corresponding to the distribution of the auricular branch of the vagus There was no tinnitus and the hearing was undisturbed Canal and tympanum were free The eruption desiccated and disappeared, leaving a few small scars The neuralgic pains (post-herpetic otalgia) persisted for a long time and were very severe Six months

later, the patient was still subject to neuralgic pains in the ear, very sharp and shooting in character and causing a distinct reflex jerk of the head. The hearing was normal.

*Comment*—This case is interesting because of the persistent and severe post-herpetic otalgia and the localization of the herpetic vesicles, posteriorly, in the cleft between the auricle and mastoid process, within the distribution of the auricular branch of the vagus (Fig 3)

CASE 4—*Herpes Zoster Oticus with Facial Palsy*—(Referred from the New York Eye and Ear Infirmary, by Dr Robert G Reese) J M, aged 19, was exposed to cold on Feb 1, 1909, this was followed by coryza and chilly sensations. The next day there were pains in the depths of the left ear, concha and mastoid region, which were so severe during the night that the patient could not sleep. On February 5, there was a paralysis of the left side of the face, but no tinnitus, and the



Fig 4 (Case 4)—Peripheral facial palsy in conjunction with an eruption of herpes zoster in the cleft between the auricle and the mastoid process, in the distribution of the auricular branch of the vagus

hearing was undisturbed (Fig 4). Examination on February 9 showed complete facial palsy with ageusia in the distribution of the left chorda tympani. Hearing was normal. An eruption of herpes zoster was distributed posteriorly in the cleft between the auricle and mastoid region (See Fig 5).

*Comment*—This case is interesting because of the situation of the eruption in the distribution of the auricular branch of the vagus, and the associated facial palsy, which I attribute to an inflammatory reaction in the geniculate ganglion of the seventh nerve.

CASE 5—*Herpes Zoster Oticus with Facial Palsy*—(Referred by Dr Josephine Walter of New York City) Miss S, aged 30, in good health. Onset the last week

in October 1909, with neuralgic pains in the right ear, occipital region and right side of the face. A few days later "a sore throat on the right side which was slightly swollen and inflamed" (Examination by ship surgeon). At the same time there appeared a small group of herpetic vesicles in the concha of the right ear. The antitragus was swollen red and tender. A right facial palsy appeared on November 6, hearing normal. November 26 the facial innervation was gradually improving on the right side although evidences of paresis in all three branches were still present hearing normal taste normal. The desiccated



Fig. 5 (Case 4) — An eruption of herpes zoster limited to the distribution of the vagus on the posteromesial surface of the auricle, and adjacent mastoid

remains of the vesicles were still evident in the conchal region, none within the auditory canal. Neuralgic pains still persisted in the ear. There was a distinct paresis of the soft palate on the affected side, and on innervation the uvula was drawn upward and to the left.

*Comment* — This case is of interest because of the localized "sore throat" on the right side and the associated paresis of the right side of the soft palate in conjunction with herpes oticus and seventh nerve palsy.

CASE 6—*Herpes Zoster with Facial Palsy*—(Referred by Dr N R Norton of New York) Miss F, aged 22 Onset Oct 24, 1909, with neuralgic pains in and about the left ear, and when severe, radiating through the left side of the face and head. From the first, there was also tinnitus aurium and a distinct sensitivity to high pitched sounds (hyperacusis). A few days later, a small group of herpetic vesicles made their appearance and were distributed on the floor of the auditory canal at the entrance to the meatus, in the concha and beneath the fold of the antihelix. On November 7, a left facial palsy appeared. Examination on November 11 showed a paralysis of the left side of the face, all branches were involved, hearing normal. Taste lost in the left chorda distribution. Tear secretion was increased on the left side (Inhalation of oil of mustard). Palate innervation normal. On November 18, facial palsy was much improved, only a trace remaining, still occasional slight pains in the ear.

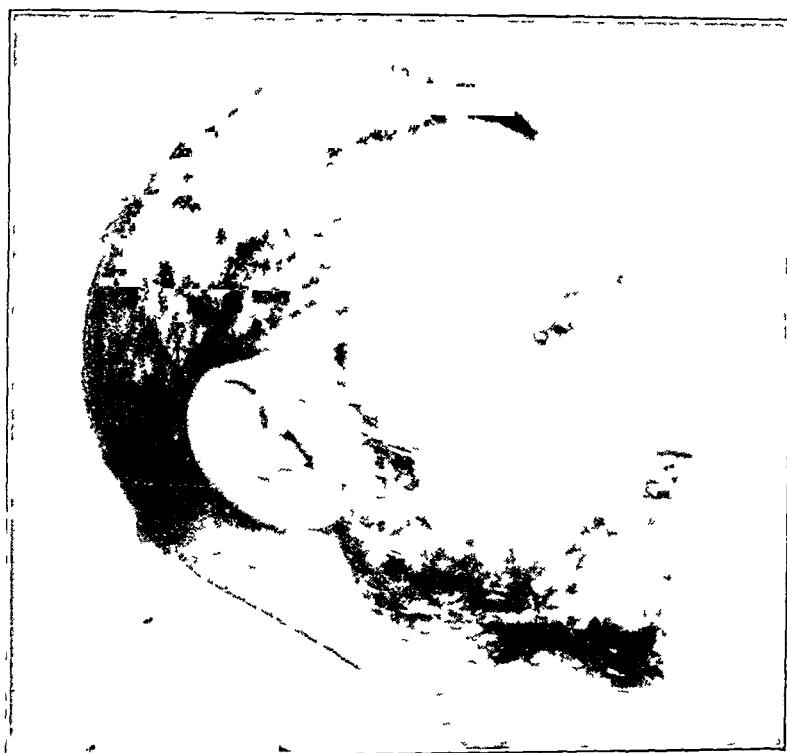


Fig 6 (Case 8)—*Herpes zoster oticus with facial palsy*. The herpetic vesicles are situated on the tragus, antitragus, concha and the lobule. Swelling and edema of the central part of the auricle.

*Comment*—In this case, hyperacusis and tinnitus aurium had definitely preceded the onset of facial palsy, and so cannot be attributed to an interference with the action of the stapedius muscle, as in oxycephaly, it may therefore be regarded as a mild expression of auditory nerve irritation.

CASE 7—*Herpes Zoster Oticus with Facial Palsy*—(Referred by Dr E G Zabriskie of New York) Mrs S K, aged 50 Onset October 29, with sharp, shooting pains in the left side of the head, in the occipital and temporal regions. On Wednesday the pains were severe and chiefly centered in the mastoid region, just behind the auricle. On Wednesday evening, a left facial palsy was apparent. No there was also an itching in the auricle and an eruption of herpes zoster.

and right ear. The pain was continuous, but was more severe at night. He had no fever, but was very uncomfortable. On October 17, he was examined by Dr. J. H. C. and found to have a vesicular eruption on the right ear, extending from the tragus to the lobule, and also on the posterior portion of the concha and the superior surface of the antihelix. There were also a few vesicles on the posterior portion of the tympanic membrane. The pain was continuous and very severe at night, the auricle was swollen and tender. On October 18, a right facial palsy appeared, and tinnitus with diminution of hearing on the affected side (Fig. 7). Examination on November 1, complete right facial palsy.

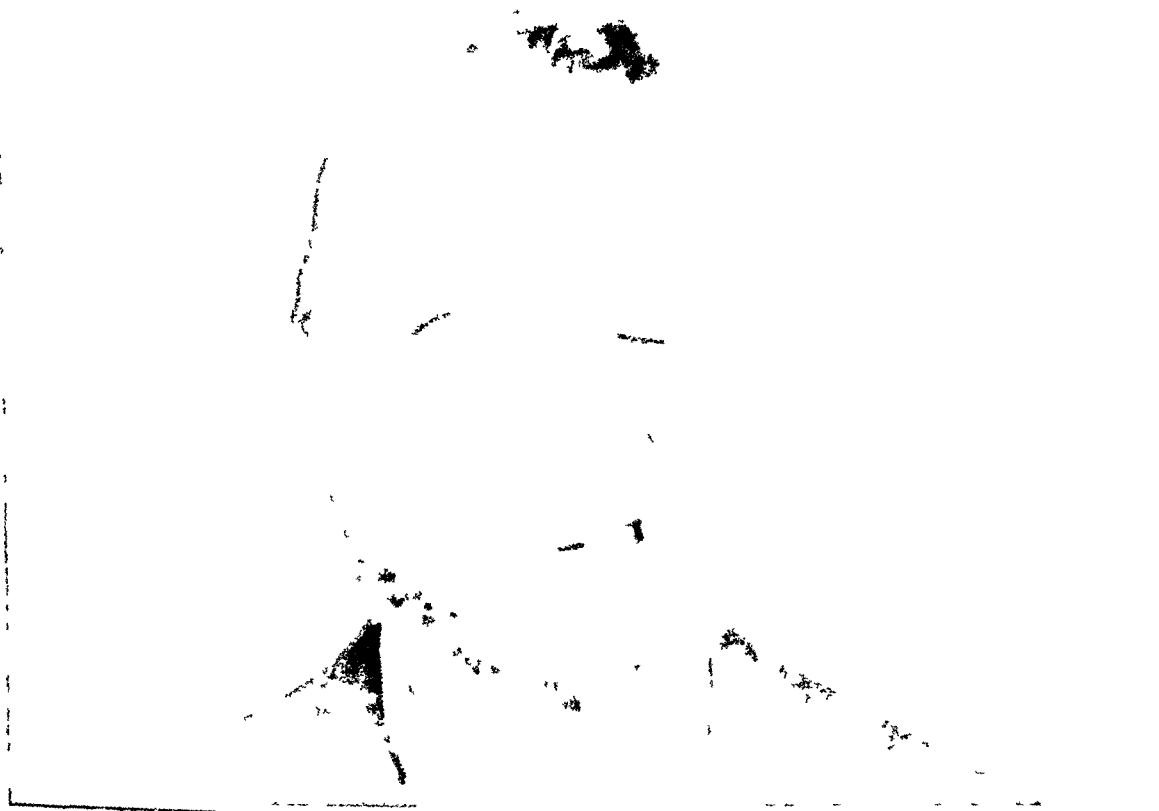


Fig. 7.—Case 8.—Complete right-sided facial palsy, top, 10/18/1907, in the general type, occurring in connection with the herpetic auricular disease.

**CASE 8—Herpetic Disease of Ear and Face.**—Entered by Dr. J. Abramson of New York, on Oct. 17, 1907, and reported on Oct. 18, 1907, with deep-seated pains in the mastoid region and depth of the right ear. The next day the auricle became swollen and the seat of an herpetic eruption. Small groups of vesicle were situated on the tragus, antitragus and immediately below on the lobule, also a group on the posterior portion of the concha and the superior surface of the antihelix (Fig. 7). There was also a single large vesicle on the posterior portion of the tympanic membrane. The pains were continuous and very severe at night, the auricle was swollen and tender. On October 18, a right facial palsy appeared, and tinnitus with diminution of hearing on the affected side (Fig. 7). Examination on November 1, complete right facial palsy.

with reactions of degeneration, hypesthesia of the right side of the face, conjunctival reflex present. Palate innervation, normal. Tear secretion present on both sides.

Otologic examination by Dr W S Bryant, as follows. Right auricle slightly more prominent than the left. Edematous and tender, especially about the concha. Some thin crusts on the floor of the concha and antitragus. Canal much smaller than on the other side. Fundus of canal bright red, swollen and leaking bloody serum. The membrana tympani anterior half clear, posterior half involved in swelling of canal. Lumen of inner end of canal reduced to one third of the size of its fellow. Slight tenderness half an inch behind mastoid antium. Left ear shows advanced chronic middle ear catarrh with retraction and contraction of the drum membrane and some thickening. Light reflex nearly absent. Tinnitus in right ear only. Functional tests. High tone limit, right ear, 12,500 vib., left ear 10,600 vib. Low tone limit appears to be the same in both ears, between 67 and 59 vibrations. Fork, 512 single vibrations was referred from all parts of the head to the right ear. Fork 512 vibrations on the right mastoid 8/30 seconds, on left mastoid 5/30 seconds. Watch right ear was 4/36, left ear was 11/36. Val salva's inflation and politzerization negative in both ears. Catheterization showed a clear tube and free tympanic cavity on the right.

Summarizing, it can be said that chronic middle ear catarrh and senile changes of both ears are marked. There is no indication that the two middle or inner ears differ very much in their condition. The sound conducting mechanisms of the membrane and canal are affected on the right, with meningitis and otitis externa diffusa.

On April 3, 1908, there was persistent weakness of the right facial innervation with secondary contractures, hearing normal, no pain.

**CASE 9—*Herpes Oticus with Facial Palsy***—(Observation by Dr Sidney I Schwab of St Louis.) Miss D, aged 28. A previous history of old ear trouble of many years' duration on both sides. Patient was in her usual health up to April 28, 1908, when she awoke in the morning with pain in the right ear and mastoid region. This pain was accompanied by headache and some general weakness. Pains in the ear continued and were very severe. Examination on May 2 revealed a herpetic eruption in the external auditory canal, and on the concha. There was also a right facial palsy. Pain sense on the right side of face was diminished in the trigeminal distribution (Hypalgesia).

Otological report as follows. Both ears. Bone conduction decidedly better than air conduction (Only C4 heard better by air conduction). Length of time tuning fork heard by air decidedly decreased bone only slightly decreased. Fork placed on median line of head always lateralized to right side.

Left ear. Old kidney-shaped perforation in drum below handle of hammer which was partly destroyed. Speech 6.0 meters, whisper 0.5 meter. After politzerization, speech —6.0 m whisper more than 0.75 meter.

Right ear. 6.8 small ulcers in different stages of resolution seen on the auricle, chiefly on the crest of the antihelix, although there were a couple in the concha. The meatal walls were slightly redder than normal. The drum showed an old cicatrix, occupying the anterior inferior quadrant and part of the posterior inferior. The remainder of the drum was diffusely reddened, except for a small red spot over the handle of the hammer just below the short process. The drum was, as a whole, retracted, the handle being almost horizontal. Hearing, speech —0.05 meter, whisper not heard, after politzerization, speech 0.5 plus meter whisper not heard. The sensitiveness of the meatus and drum was normal. The mastoid was hypersensitive, especially over the antium.



which I shall base the separation of these otic zones has been considerably abbreviated for purposes of presentation, and is anatomical, embryological and clinical in its nature.

#### ANATOMICAL CONSIDERATIONS (THE SENSORY INNERVATION OF THE EXTERNAL EAR)

The external ear is distinguished by a peculiarly complex and intricate sensory innervation, four cranial and two spinal ganglia participating in its nerve supply. The difficulty of the subject is still further increased by the small, almost vestigial distributions of some of the ganglia represented, as well as by the normal variation and overlap of sensory zones, which is considerable in this region.



Fig. 8.—Outlines of the auricular portion of the trigeminal field determined by the line delimiting tactful anesthesia (After Cushing.)

The nerve-supply of the auricle may be summarized as follows. The Gasserian ganglion is represented by auricular filaments which arise from the auriculotemporal branch of its third division, the geniculate, by auricular fibers, which emerge with the facial at the stylomastoid foramen, the exact course and distribution of which are at present unknown, the petrous ganglion of the ninth, and the jugular ganglion of the tenth, by their respective auricular branches, and the second and third cervical ganglia, by the auricular branches of the cervical plexus. There are numerous anastomoses between these various nerves, and I would especially emphasize those between the auricular branches of the ninth and



its upper mid portion, ascends over the edge of the helix to the outer face of the ear which is crossed behind the fossa triangularis to the antihelix, the ridge of this latter structure it follows passing around the posterior margin of the concha to the incisura intertragica, the line usually dipping in somewhat on the inner face of the antitragus, from the incisura intertragica, 5 mm or more below the point of emergence of the trigeminal line for touch, it passes out on to the cheek, usually in a forward and downward direction”

If the fields of the trigeminus and of the second and third cervical ganglia are now brought together and adjusted on the auricle, there is found to exist an intervening area consisting of the concha, fossa of the antihelix, tip of the antitragus, and the posterior portion of the meatus, auditory canal and tympanic membrane. This small intervening area, I believe, contains the somatic or auricular representations of the geniculate, glossopharyngeal and vagal ganglia.

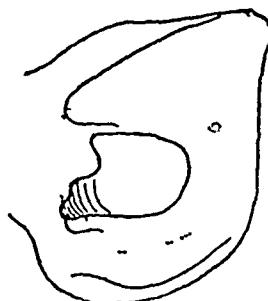


Fig 10.—Within dotted lines lies the ‘completely delimited area of the auricular branch of the vagus’ determined experimentally for the macaque (Sherrington.)

Sherrington<sup>6</sup> has succeeded in demonstrating the existence of a similar area in monkeys by the experimental method of “remainingesthesia.” His description of this field is in part as follows (Fig 10)

The field has been completely delimited in two experiments only, the operation required for revealing it is somewhat severe. Lying, as the small field does, wedged in between the large fields of the fifth cranial and the third cervical, and, as it were, imbedded in the anterior part of the field of the second cervical it is, in order to isolate it, necessary to sever the fifth cranial at its origin, and also the highest three cervical nerves inside the vertebral canal. When this has been successfully accomplished, a patch of esthetic skin is easily demonstrable on the ear. It includes and immediately surrounds the external auditory meatus. Its shape and size, in the experiment carried out on it, were almost identical. It takes in practically the whole of the concha, the antitragus, part of the tragus and part of the antihelix, also part of the fossa of the antihelix. Its limits can be better realized from the figure than from verbal description. The surface inside the external auditory meatus was sensitive in my experiments as far inward as could be tested with an ordinary probe.

<sup>6</sup> Sherrington, C S Experiments in Examination of the Peripheral Distribution of the Fibers of the Posterior Roots of Some Spinal Nerves, Phil Trans Royal Soc of London, Series B, 1898, etc, 64



The dissection method therefore shows that the fifth is concerned in the innervation of the anterior portions of the tympanic membrane, external auditory canal and meatus, and the vagus, in the innervation of the posterior portion of the tympanic membrane and auditory canal, together with a strip on the posteroomesial surface of the auricle. The exact boundaries of their respective distribution within the canal is still a matter of dispute.

This leaves the concha, tip of the antitragus, a portion of the antihelix, and the fossa of the antihelix still unaccounted for, and the innervation of this area I believe to be related in part to the geniculate ganglion of the seventh.

#### EMBRYOLOGY

Developmental studies in the human embryo and the lower forms of life have contributed very largely to our knowledge of the morphology of the cranial nerves, their origin and distribution. In the light of these investigations, the seventh, ninth and tenth nerves are to be regarded as branchial nerves, which in the lower vertebrate forms stand in immediate relation to their respective visceral clefts and arches. The seventh is the nerve of the first visceral cleft. From this cleft and its adjacent arches are developed the structures of the external ear, the tympanic membrane closing and separating it from the first visceral pouch. The anterior or mandibular arch lies within the area of the trigeminus, and gives rise to the tragus and the crura of the antihelix of the adult ear, which is in accord with Cushing's studies and the results of the dissection method (Fig. 11).

The posterior, or hyoid, arch is innervated by the facial system. From this arch are developed the auricular tubercles of the antitragus, antihelix and the lobule. As the concha auris and external auditory canal are similarly related to the first visceral cleft, they too may be regarded as falling in part within the area of innervation of the seventh nerve (Fig. 12).

The auricular branch of the vagus is considered by some embryologists to be a remnant of the so-called lateral line (*ramus lateralis*), and has been traced as far forward as the first visceral cleft, where, as we have seen, dissection method has shown it to be partly distributed (auditory canal).

Embryology, therefore, shows that the tragus and crura of the antihelix are situated within the area of the trigeminus, the antitragus, lobule, antihelix, concha, and part of the auditory canal, within the area of the facial. The auricular branch of the vagus may be traced anteriorly into the first visceral cleft.

These various anatomical facts may be summarized as follows:

There exists on the auricle a cutaneous zone which is independent of the trigeminal and cervical innervation of this structure. This area is innervated by fibers arising from the geniculate ganglion of the seventh, the petrosal ganglion of the ninth, and the jugular ganglion of the tenth. It appears probable from the dissection method that the auricular branch of the vagus, which also includes the auricular branch of the glossopharyngeal, participates in the innervation of the posterior portion of the tympanum and auditory canal, together with a strip on the posteromesial surface of the auricle and adjacent mastoid.

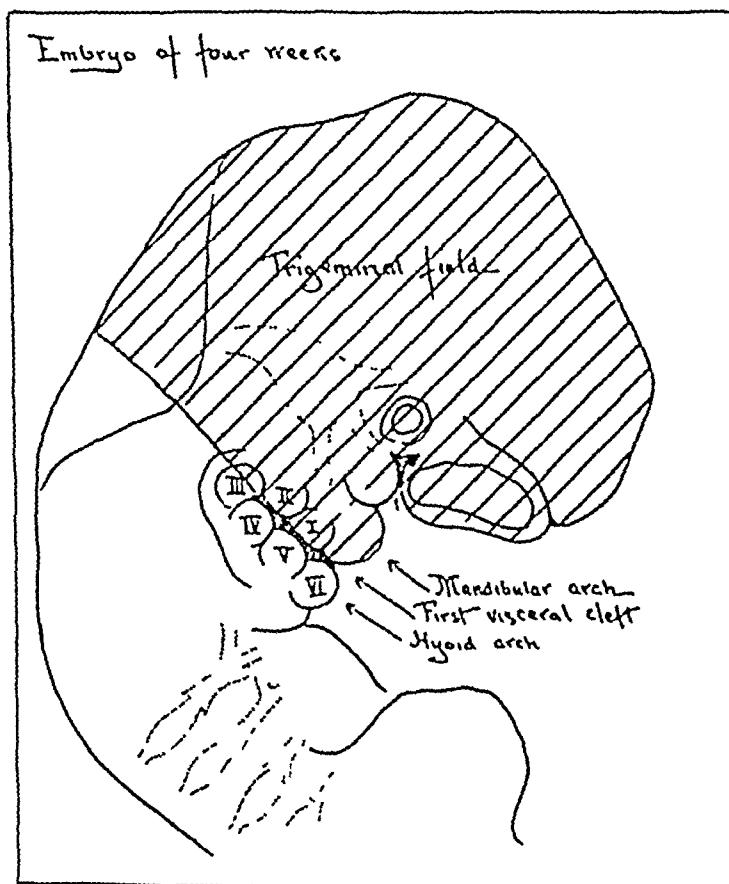


Fig. 11.—Relation of the auditory tubercles of the mandibular arch to the trigeminal field, in an embryo of four weeks (After Cushing).

It also appears probable that the concha, antihelix, fossa of the antihelix, antitragus, incisura intertragica, and a portion of the lobule are in part innervated by the geniculate ganglion, the sensory fibers of which course in the trunk of the seventh, probably reaching the external surface of the auricle with the branches supplying the minute muscles of the external ear. In this relation one must consider, however, the anastomoses which take place between the seventh, ninth and tenth nerves.

This sensory innervation of the facial receives a further corroboration from its developmental relation to the first visceral cleft and the auricular tubercles of the posterior or hyoid arch. I believe, therefore, that the ganglion of the seventh nerve has a representation on the external ear between the zones of the Gasserian and cervical ganglia, also that the

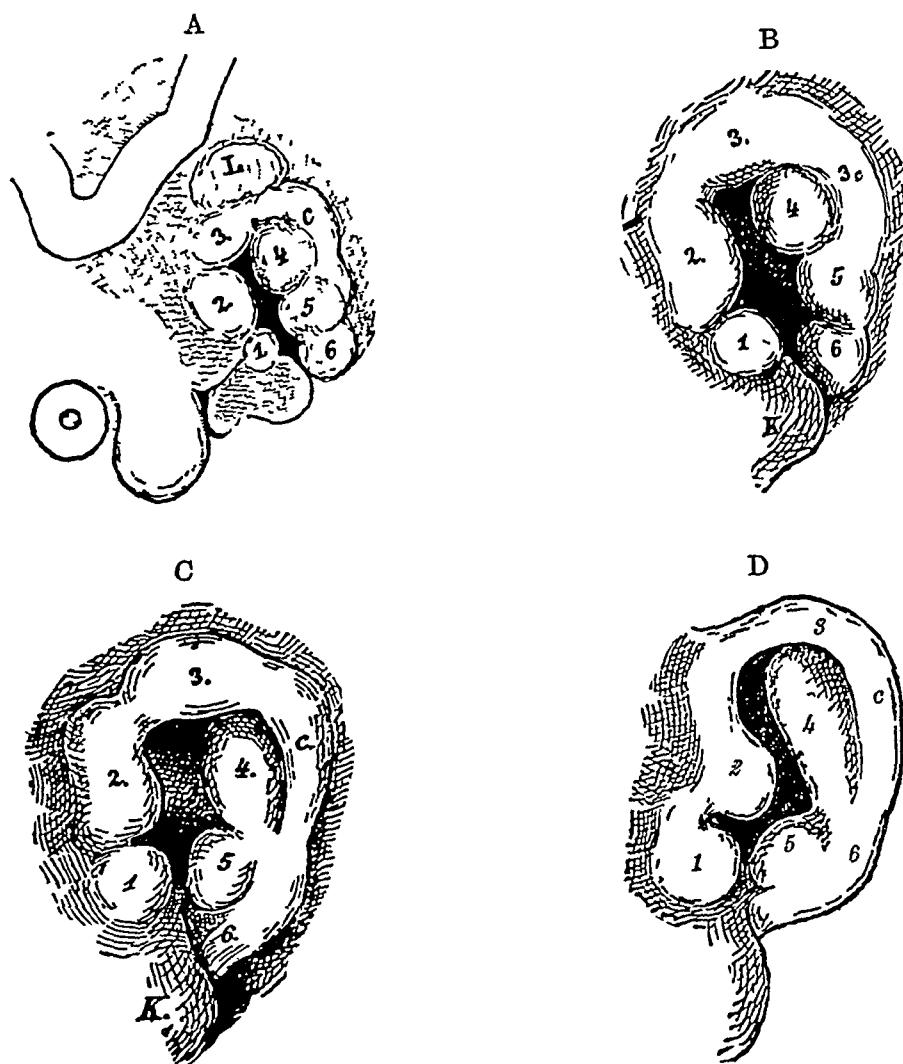


Fig. 12.—Sketches showing the development of the parts of the external ear from prominences on the mandibular and hyoid arches (His). Variously magnified. A, embryo at the end of the first month, B, embryo of thirty-five days, C, embryo of thirty-eight days, D, embryo at the end of the second month. 1, tuberculum trigium, 2, tuberculum anterius helicis, 3, tuberculum intermedium helicis, 3c and c, cauda helicis, 4, tuberculum antihelicis, 5, tuberculum anti-trigium, 6, tuberculum lobulare, L, in A, auditory vesicle, K, lower jaw.

ganglia of the glossopharyngeal and vagus are represented in part on the posterior portion of the tympanum and auditory canal, as well as on the posterior mesial surface of the auricle and adjacent mastoid region.

## THE "HERPES ZOSTER" METHOD

The herpes zoster method of determining the sensory representation of spinal ganglia has been used so successfully by Henry Head and his collaborators that I need not dwell on its many advantages as a means of ascertaining the sensory zones of small and obscure ganglia like those under consideration which are also of the spinal type. It is very evident that a study of those cases of true herpes zoster in which the eruption is confined to the auricular area in question would furnish evidence of fundamental importance in clearing up this subject. With this end in view I have analyzed twenty-seven cases of true herpes zoster oticus in which the eruptive manifestations were limited to small areas on the external ear. These I believe are dependent on herpetic inflammations (*posterior poliomyelitis*) in one or more of the three ganglia represented in this area, the geniculate, glossopharyngeal and vagus. In five of these cases the vesicles were localized either on the tympanic membrane alone or upon the posterior wall of the auditory canal. In four of the cases they were situated on the posteromesial surface of the auricle and adjacent mastoid region. It will be observed that the localization of the vesicles in both of these groups correspond in their distribution to the auricular branches of the jugular ganglion of the vagus. For reasons already stated it is probable that the ganglion of the ninth may also be concerned in their production.

In eighteen of the cases the eruption was distributed in what I regard in part as the geniculate area on the external ear, i.e., the external meatus, concha, tragus, antitragus, antihelix and fossa of the antihelix and the upper portion of the external surface of the lobule. This representation of the geniculate on the external ear is corroborated by the occasional presence of hypesthesia in the region of the concha in cases of recent peripheral facial palsy.<sup>10</sup>

From the "herpes zoster" evidence I believe that we are justified in drawing the following conclusions. True herpes zoster oticus is dependent on a posterior poliomyelitis of the geniculate, glossopharyngeal or vagal ganglia. The ganglia of the tenth and the ganglia of the ninth are represented in part on the posterior portion of the tympanic membrane and auditory canal, as well as on the posteromesial surface of the auricle and adjacent mastoid region.

The zoster zone of the geniculate ganglion is represented on the external surface of the auricle, intercalated between the zone of the trigeminus in front and the cervical ganglia behind. From the relation

<sup>10</sup> Hunt, J. Ramsay. The Sensory System of the Facial Nerve and Its Symptomatology, *Jour. Nerv. and Ment. Dis.* 1909, **xxxvi**, 321.

which the facial bears to the first visceral cleft (the auditory canal) it is very probable that the zone of the geniculate dips into the auditory canal as far forward as the tympanic membrane, in the same manner as do the auditory strips of the trigeminus and glossopharyngeal-vagus.

As I have already indicated, a considerable allowance must be made in these zones, as I have outlined them, for anatomical anomalies of various kinds, and for the normal physiological variation and overlap of sensory areas. Furthermore, these sensory areas are small and, like the minute muscles of the external ear, must be regarded as more or less vestigial in character. In other words, as remnants of sensory zones, which are gradually fading away under the overlap of larger and more important sensory systems.

### 3 THE PARALYTIC COMPLICATIONS OF HERPES ZOSTER OTICUS

In cases of herpes zoster oticus, facial paralysis and auditory symptoms may accompany or follow the eruption. The face on the affected side may be paralyzed without symptoms referable to the auditory nerve, auditory symptoms also may occur without facial palsy.

Among the twenty-seven cases of my series with herpes oticus, facial and auditory symptoms were both present in six cases. Facial palsy occurred alone in six, and auditory symptoms in three cases. The facial paralysis was always complete, involving all three branches, while the auditory symptoms varied in intensity from hypacusis with tinnitus aurium to the severest manifestations of Ménière's syndrome. The general constitutional reaction was in the greater number of cases a very trivial one. In some, however, there was considerable prostration, accompanied by headache, rigidity of the neck, with nausea and vomiting. Nausea and vomiting were so severe and persistent in some instances, as to suggest a disturbance of the vagus nerve, which was further confirmed by the associated bradycardia.

This group is of such unusual clinical interest, that I append the abstracts of some very typical cases.

CASE 10.—*Herpes Zoster Oticus, with Vomiting and Bradycardia*—(Observation by Buys<sup>11</sup>) A girl, aged 17. Onset with headache and vomiting. Headache very severe and accompanied by stiffness of the neck, frequent vomiting and photophobia. No fever, no delirium. Pulse was slow and irregular, on the fourth day, the pain subsided somewhat and settled in the mastoid region of the right side. Hearing was diminished and the auditory canal was tender on the introduction of the otoscope. The next day an eruption of herpes appeared on the antitragus and lobule of the right ear. The day following this a flesh crop of vesicles

11 Buys Eruption herpétique du pavillon, Bull Soc belge d'otol., laryngol et rhinol., 1898.

appeared on the internal face of the lobule and pinna. In the course of a few days the pain subsided and hearing was restored. All traces of the eruption disappeared in fifteen days.

*Comment*.—This case is noteworthy because of the distribution of the eruption in the zonal areas of the geniculate and vagal ganglia, and because of the associated bradycardia with frequent vomiting, suggesting a disturbance of the functions of the vagus.

The following observation by Mignon<sup>12</sup> is of interest, as the eruption corresponds to the auricular distribution of the vagus nerve. There was an associated deafness but no symptoms of vagus irritation are recorded.

CASE 11.—Patient, a woman, onset January 3 with severe pains in the left ear, posterior surface of the auricle, and the mastoid region. Fever and malaise. Two days later tinnitus in the left ear and deafness with herpetic vesicles situated on the outer third of the auditory canal. The pinna was congested, as was also the skin over the mastoid. The next day herpetic vesicles were noted on the mastoid and the postero internal surface of the auricle. Tympanic membrane normal. The deafness on the left side was of the nervous type, accompanied by severe tinnitus. No nystagmus, no vomiting, no vertigo, no signs of facial palsy. In a fortnight the hearing had improved considerably and at the end of a month was entirely normal.

CASE 12.—*Herpes Zoster Oticus with Seventh Nerve Palsy, Auditory and Vagus Symptoms*.—(Observation by Hammerschlag<sup>13</sup>) Man aged 25. On July 7 exposure to cold, while overheated. The next morning a sore throat which increased during the day and continued for five days. On July 17, the soreness of the throat had disappeared but vomiting set in and persisted during the day. The vomiting occurred without retching, and immediately after the ingestion of food. July 19 he was able to retain milk in small quantities. On this day there appeared sudden sharp pains in the right ear, radiating through the whole side of the head. At the same time there was a weakness of the right side of the face and severe vertigo, aggravated by movements of the head. From this time the patient had to be assisted in walking, owing to the disturbances of equilibrium and a tendency to fall to the left. On July 20, vomiting again set in, and even the slightest nourishment was rejected. On July 25 the respiration was regular and deep, twenty to the minute, pulse frequency, 48. Laryngological and rhinological examinations were negative. July 27, there is still vertigo and vomiting. Pupils are normal, nystagmus in the extreme position. Pain sense is diminished on right face in trigeminal area, corneal and conjunctival reflexes are diminished on the right also, the auditory canal reflex diminished on the right. Points of exit of the fifth nerve are tender. There is right facial palsy. Innervation of palate normal, taste sense is diminished on the right. Tear secretion is present. Pulse is 72 and regular. July 28, the left tympanum is normal, the right is concealed by dusting powder. In the auditory canal, especially at the entrance, there are several small scabs and in the cymbæ conchæ a small scar, these are the remains of an eruption of herpes zoster. The hearing is diminished on the right side and is of the nerve type. Acutometer, left side, 12 meters, right side, 75 cm., bone conduction heard only on the left. Weber's test lateralizes to the left. Eye grounds are normal. During the last few days, the above symptoms have diminished in intensity.

12 Mignon Zona otique, Bull de laryngol, otol, et rhinol, 1909, vii, 196.

13 Hammerschlag Die rheumatische Affectionen der Gehörnerven, Arch f Ohrenh, 1901, hi, 7.

August 4 Acumeter on the right side, 1 m., 30 cm. Slight facial weakness is still apparent and the taste is still diminished on the right. Gait practically normal. Sensation of face slightly hypesthetic. The auditory canal reflex still diminished. There is tinnitus aurium, the right side of the face shows diminished faradic with normal galvanic responses.

**CASE 13—*Herpes Zoster Oticus with Facial Palsy and Auditory Symptoms—*** (Observation by Hammerschlag<sup>14</sup>) Man, aged 32. On March 14, while the patient was walking in a snow storm right side of the face was exposed to severe cold. Five days later there were chills and on March 20, onset with vomiting and vertigo—objects rotating from right to left.

On the morning of the 20th, on awaking, patient had a headache and severe pains in the right ear accompanied by roaring sounds. A weakness of the right side of the face was also apparent. The pain radiated to the forehead, eye and to the teeth of the upper and lower jaw. Sensation of the right side of the face was diminished. March 22, the tear secretion was absent on the right side, there was a right facial palsy, and nystagmus followed lateral movements. In the fossa of the helix on the lobe of the ear and on the tragus, there was an eruption of herpes zoster. There were no vesicles within the auditory canal. Hearing was diminished on the right, the watch tick at 35 cm. not heard on the mastoid. There was considerable disturbance of the equilibrium both in standing and walking. The gums, above and below on the right side, were a little swollen. The conjunctival reflex was absent on the right. Sensation of taste was lost on the right.

March 31, face was improved. Hearing on the right was 40 cm. by watch, bone conduction for watch, still absent.

April 1, there was still vertigo and tinnitus, tear secretion normal.

April 3, tinnitus in the right, and occasional shooting pains. Bone conduction had improved.

April 5, taste improved.

April 25, patient complained of cold sensation in the head and constant tinnitus in the ear. The upper branch of the seventh showed improvement, none of the lower branch. The gait was much better. The bone conduction on the right was absent, the watch was heard only on contact, for several days past there had been diplacusis on the right side, and a disagreeable sensation was produced by musical tones.

**CASE 14—Observation by Newmann** A man, aged 44. Onset with pains in the right ear and occipital region, accompanied by vomiting and objective vertigo. Two days later, herpetic vesicles appeared in the external auditory canal. The next day there was facial palsy, the pulse was slow, the temperature 38.8°C. The auricle was red on its superior portion and the skin was thickened. Functional tests showed complete deafness to fork and voice in the right ear. The vestibular apparatus was inexcitable. At the end of three weeks the vestibular apparatus still was inexcitable, and absolute deafness with facial palsy persisted. The case was presented as one of rheumatismal cerebral polyneuritis.

#### 4 THE ZOSTER ZONES OF THE GLASSOPHARYNGEAL AND VAGAL GANGLIA WITHIN THE BUCCAL CAVITY

The glossopharyngeal nerve has two ganglia situated on its root, the ganglion petrosum (Andersch), and a small accessory ganglion, the ganglion of Ehrenbüttel, both are homologues of the spinal ganglia, are

<sup>14</sup> Hammerschlag Beitrag zur Casuistik der multiplen Hirnneurien Etiologien, Arch f Ohrenh., 1898, xlvi, 1

composed of unipolar cells, and therefore belong to the ganglionic chain which is liable to the specific inflammation of zona (Fig. 13). These ganglia have a sensory representation on the auricle and also an intra-oral zone situated on the postero-lateral surface of the tongue, the pillars of the fauces, tonsil and the adjacent pharyngeal region.

The pneumogastric nerve has also two root ganglia—the ganglion jugulare and the ganglion plexiforme (Fig. 13). The cells of these ganglia are also of the unipolar or spinal type. The plexiform ganglion is situated extracranially and is peculiar in that it is composed of a series of small scattered groups of cells which produce an elongated swelling of the nerve trunk about 15 mm. in extent. This plexiform arrangement is caused by the entrance into the trunk of the vagus of the inter-



Fig. 13.—The ganglia of the ninth and tenth nerves and their auricular branches. (1) spinal accessory nerve, (2) glossopharyngeal nerve, (2') ganglion of Andersch, (3) vagus nerve, (3') ganglion jugulare, (4) facial, (4') auricular branch of facial, (5) auricular branch of vagus, (6) anastomosis between the auricular branches of the facial and vagus nerves (Testut's Anatomy).

nal branches of the accessorius nerve sometimes called the external or motor root of the vagus. It is important to note that these motor fibers of the accessory nerve destined for the muscles of the larynx, enter the vagus below the jugular ganglion, as a descending series of small branches. This morphological distribution may explain the apparent absence of laryngeal palsies in posterior poliomyelitis of the vagal ganglia.

In addition to an auricular representation, on the tympanum, auditory canal, and postero-mesial surface of the auricle, these ganglia have also

an intra-oral zone situated on the root of the tongue, the structures at the entrance to the larynx, and the adjacent pharyngeal region (Fig. 14)

It may be remarked that these respective sensory areas of the glossopharyngeal and vagus nerves within the mouth cavity are by no means definitely determined, and there is also every reason to believe that a considerable variation and overlapping exists

In discussing the zoster zones of the auricle, I stated that a separation of the glossopharyngeal and vagus representations is impossible, as the

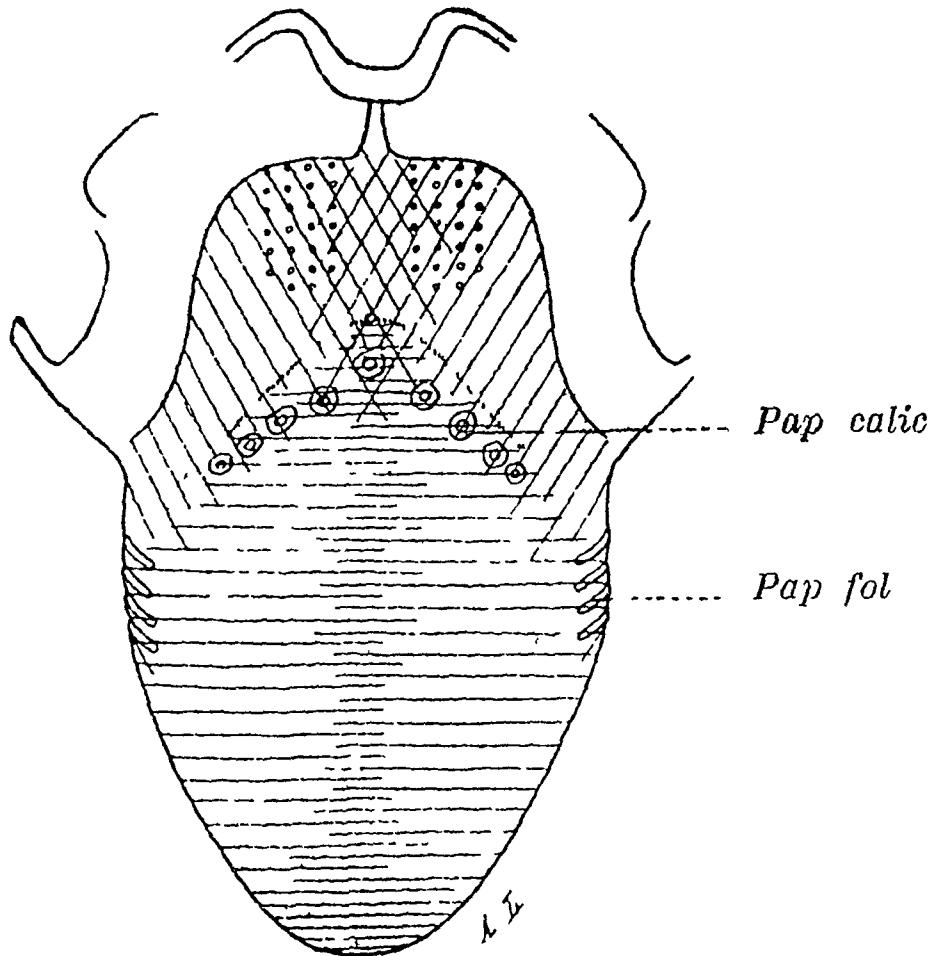


Fig. 14.—Sensory innervation of the tongue (after Zander). The lingual distribution is indicated by transverse lines, the glossopharyngeal by oblique lines and that of the pneumogastric by dots

auricular branch of the ninth joins the auricular branch of the tenth soon after leaving the ganglia. Their respective cutaneous destinations are therefore unknown and must be considered together.

In the posterior recesses of the buccal cavity, where these ganglia are also represented, this is not the case, and the "dissection method" gives

a very fair idea of their respective mucous membrane distributions. An exception to this is in the upper pharynx where the various pharyngeal branches are lost in the mazes of the pharyngeal plexus.

The glossopharyngeal nerve according to the best anatomical authorities, sends filaments to the mucous membrane covering the posterior margin of the soft palate, the anterior and posterior pillars of the pharynx, the tonsil, the posterolateral surface of the base of the tongue also to the pharyngeal plexus.

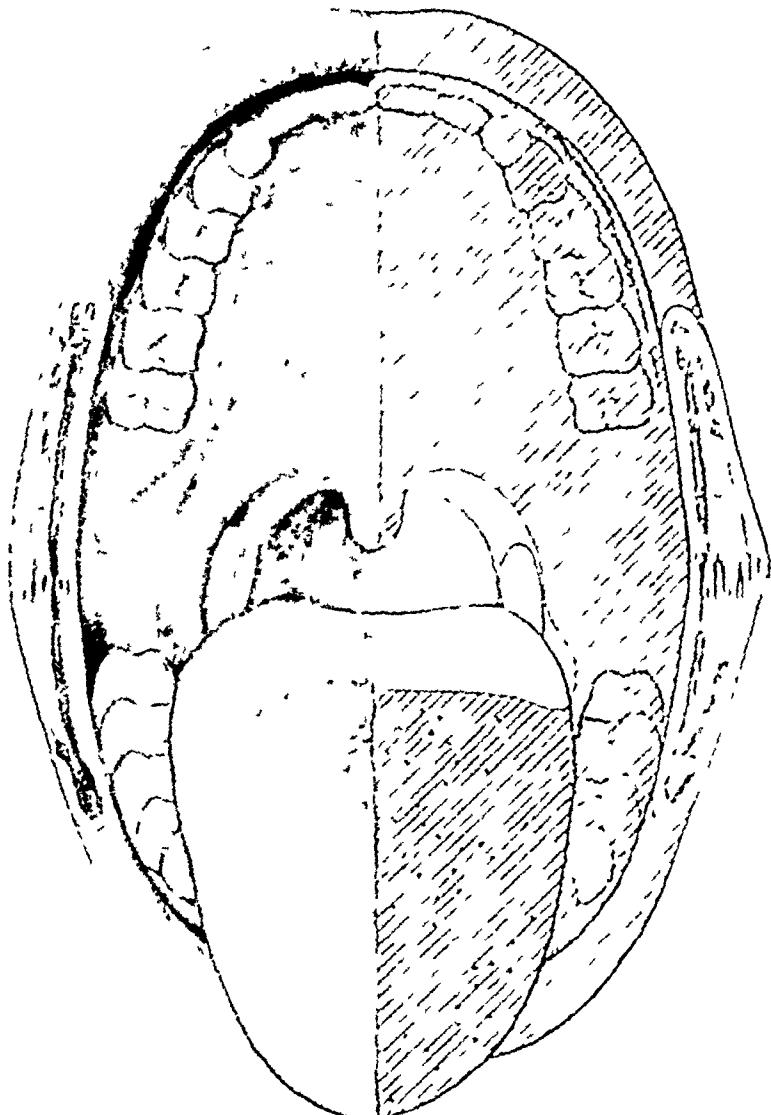


Fig. 15.—Posterior limits of the intrabuccal field of the trigeminus, after extirpation of the Gasserian ganglion (Harvey Cushing).

From the vagus nerve sensory filaments pass to the mucous membrane covering the epiglottis, arytenoid eminences, and the aryteno-epiglottidean folds, also to a wedge-shaped area at the base of the tongue, situated immediately in front of the epiglottis (Fig. 14). The vagus also sends branches to the pharyngeal plexus.

The intra-oral zone of the glossopharyngeal is therefore intercalated between the trigeminus in front and the vagus behind, and corresponds roughly to a semilunar strip passing from the posterior margin of the soft palate over the pillars of the fauces, the tonsils, and the posterolateral surface of the tongue, including also an unknown area of the upper pharynx (Figs 14 and 15).

The intra-oral zone of the vagus is situated more posteriorly and corresponds to a small wedge-shaped strip at the base of the tongue, which is continued over the epiglottis, aryteno-epiglottidean folds and the arytenoids, including also an unknown representation in the upper pharynx.

It will be observed that both the ninth and tenth nerves give off branches which unite with the sympathetic to form the pharyngeal plexus. Their respective distributions in this region are unknown and must be considered together.

#### HERPES ZOSTER PHARYNGIS AND HERPES ZOSTER LARYNGIS

Laryngologists have recognized for many years the occurrence of herpes zoster on the pharynx and on the larynx. In the rather voluminous literature of this subject, these cases are variously described as herpes pharyngis, herpes gutturalis, angina herpetica, and the herpes laryngis.

The cases may be sharply divided into two distinct groups, one a pseudoherpes, the other a true herpes or zona. In the latter group of cases, the eruption is unilateral and corresponds to a definite neural distribution, while in pseudo herpes, the eruption is not a zona in the true sense of that term, the appearance of an eruption being produced by closure of the glandular ducts with retention of their secretion.

In such cases the eruption is bilateral and disseminated, and is commonly distributed over the soft palate, uvula, pharynx, epiglottis, arytenoid cartilages, and aryteno-epiglottidean folds. There is also usually a considerable degree of inflammation, with edema of the mucous membrane, and the dysphagia and dyspnea are often extreme.

The pseudo-herpes I have entirely excluded, and will confine my remarks to the pure cases of unilateral herpes of the pharynx and larynx. These cases compared with the other varieties are infrequent, but I believe less so than might be inferred from a perusal of the literature. The constitutional symptoms are often very slight and the eruption particularly evanescent on mucous surfaces, the vesicles breaking down rapidly under the heat and moisture of the mouth, leaving small whitish or yellowish flecks very unlike our usual conception of an herpetic eruption. For this reason they may readily be overlooked, or their real nature not detected.

Another source of error is the small area of the zoster zones and their inaccessibility. I regard it as very probable that many acute unilateral palsies of the face, palate and even the larynx, coming on after exposure to cold, and called "rheumatic," belong in this group the paralytic symptoms following herpetic inflammation of their respective ganglia. This is probably also true of similar cases of obscure toxic origin.

### 5 THE COMPLICATIONS OF HERPES ZOSTER PHARYNGIS AND LARYNGIS

#### THE PARALYTIC COMPLICATIONS OF HERPES ZOSTER PHARYNGIS

Most systematic writers in their descriptions of herpes zoster pharyngis, mention paralysis of the palate as an occasional complication. Eichhorst<sup>15</sup> states that in herpes pharyngis with unilateral eruption patients often complain of a very bad taste sensation in the affected region, and in one case he observed paralysis of the palate. In another case the eruption had a unilateral distribution on the posterior surface of the uvula and was visible only with the laryngoscope. Dr Isadore Abramson<sup>16</sup> saw in Oppenheim's clinic in Berlin a case of unilateral herpes zoster pharyngis the eruption situated on the tonsil and posterior margin of the soft palate in which there was an associated facial paralysis on the corresponding side.

In two of my cases of herpes oticus with facial palsy there was an associated paralysis of the soft palate on the affected side. It seems to me probable that such palatal complication may be due to an inflammatory reaction in the glossopharyngeal or vagal ganglia, causing this slight defect in the innervation. Should this be verified in a sufficient number of cases, it may throw an important side-light on that much-mooted question of the involvement of the soft palate in Bell's palsy.

**CASE 15—Herpes Zoster Pharyngis with Facial Palsy and Paresis of the Soft Palate—(Personal observation.)** A man aged 23, tailor, no venereal history, excessive cigarette smoker for some years. Onset Monday Jan 10, 1910, with pain in the left side of the throat. For one week previously he had not felt well, had headaches, chilly sensations and malaise. The pain and soreness in the left side of the throat continued with increasing severity on Tuesday, Wednesday and Thursday of the same week. On Sunday January 16, there developed a left facial palsy, at the same time there was considerable pain in the left ear and mastoid region, no auditory symptoms, no nausea or vomiting.

On examination, January 17, at the Cornell Neurological Clinic, the patient complained of great soreness of the throat and pain chiefly on the left side, with

<sup>15</sup> Eichhorst, H. Spezielle Pathologie und Therapie (Herpes Pharyngis), 1897, iv, 268.

<sup>16</sup> Personal communication.

difficulty of deglutition, also sharp pains in the left ear and mastoid region, radiating to the temple and the occiput. There was complete left facial palsy, hearing normal no signs of herpes about the face, neck, auricle or auditory canal.

Laryngoscopic examination (Cornell Clinic) showed that the uvula was enormously swollen and edematous, and could be inspected only by being brought forward onto the dorsal surface of the tongue, by means of a probe. A few herpetic vesicles were visible on its left side, as well as along the left anterior pillar of the fauces. The tonsils were not enlarged and not inflamed. The posterior pharynx was congested. The entrance to the larynx was normal and no herpetic vesicles were demonstrable. A swollen and tender gland was palpable, beneath the left angle of the jaw.

Jan 18, 1910 Laryngoscopic examination by Professor Newcomb. The edema and swelling of the uvula still great but diminishing. In the left faucial region, along the anterior pillars, small round erosions were visible. Larynx was normal, and free from herpes or erosions.

January 19 Pain was still severe in the left side of the throat, ear and mastoid region. Otological examination was negative. The innervation of the soft palate appeared normal. Tear secretion was increased in the left side (oil of mustard). Pulse rate was 90, heart sounds normal. Sensation of the face and ear were normal.

January 20 Constant pain in the left ear and mastoid. Slight tinnitus, not constant. Hearing normal. Left facial palsy was complete.

January 21 Sense of taste was preserved on the left side of the tongue in both the trigeminal and glossopharyngeal distribution. It was somewhat delayed in the trigeminal area, however. Swelling of the uvula was diminishing. Innervation of the palate appeared normal.

January 24 Inspection of the soft palate revealed a definite droop of the left palatal arch, and on innervation a definite defect was noted on the left, the palate was lifted up and toward the right. A few small erosions were still present along the left anterior pillar and adjacent tonsillar region, and there was a burning sensation in this region after taking food. Sensation of the palate was equal on the two sides, and the palatal reflexes were present. The sensations of touch and taste in the glossopharyngeal distribution of the tongue were normal.

February 4 Slight power was returning to the left side of the face. Still pain in the left ear, pulse was 98 and regular.

February 7 Pains in left ear, radiating to mastoid, occiput and temple. Past few days patient had experienced a sensitiveness to loud sounds in the left ear. Slight difficulty in deglutition. Paresis of the left side of the soft palate still present, the raphe deviated from the median line toward the right. Facial palsy was improving. Pulse rate 102.

February 16 Pains in the ear still present, pulse 100.

February 18 Pulse 106.

March 4 Pulse 78. Weakness of the left side of palate still present, but improving. Innervation of left face was much better.

March 20 Patient was free from pain. Only slight defect in the innervation of the left side of palate was demonstrable. Movements of the face on the left side practically normal. Pulse 78. Patient discharged and returned to his occupation. The treatment consisted solely of analgesics for the relief of pain and galvanism.

*Comment*—This case is of unusual interest because of the coexistence of facial palsy, paresis of the soft palate and herpes pharyngis. The herpetic eruption was distributed on the left side of the uvula and along the anterior pillar of the fauces, i.e., within the intra oral representation of the glossopharyngeal ganglia. The facial palsy appeared on the sixth day and the defect in the innervation of the soft palate at the end of the second week. The pains were of unusual severity and

persisted for a considerable time. They were localized in the left side of the throat and the left ear. The pulse rate was high during the active period of the disease. There was no hiccup, nausea or vomiting. The patient had indulged excessively in the use of cigarettes for a number of years so that the tachycardia may have had this etiology. I do not believe however that involvement of the pneumo-gastric can be entirely excluded. I would interpret the case as one of posterior poliomyelitis involving the glossopharyngeal and geniculate ganglion.\*

In the following case recorded by Raynaud,<sup>17</sup> there were associated herpes pharyngis oticus and facialis with facial palsy, deafness, and abducens paralysis.

CASE 16.—A woman aged 52 sudden onset May 2 1875 with fever and angina. On May 6 still fever, deglutition painful and difficult. Examination of the throat revealed an herpetic eruption limited to the left half the soft palate and the anterior pillar of the same side. On May 7, several plaques of vesicles appeared on the left auricle also a few vesicles on the left side of the face. Other vesicles were situated on the concha and in the auditory canal. On May 8 there was a left facial palsy with hemianesthesia of the left side of the face also a small vesicle on the conjunctiva just above the cornea. There was also a distinct paralysis of the left external rectus and absolute deafness on the left side. From this time the symptoms remained stationary but later the abducens palsy disappeared and sensation returned to the left side of the face. The herpes disappeared in twelve days, but the facial palsy persisted with disappearance of the electromuscular contractility.

*Comment*.—This is the only case among the eighty seven of my series, in which mention is made of an ocular palsy in combination with facial paralysis or acoustic symptoms.

CASE 17.—Observation by Chauveau.<sup>18</sup> A woman aged 42. Sudden onset with fever, headache, sore throat and moderate dysphagia. A few hours later severe lancinating pains with tinnitus aurium in the left ear. Examination showed an herpetic eruption on the left tonsil, left side of the palate and uvula none on the larynx. The auricle and auditory canal were free from eruption, but two vesicles were seen situated on the posterior part of the tympanic membrane. There was also a herpes labialis.

*Comment*.—In this case the eruption in the ear and throat is situated within the somatic and splanchnic zones of the glossopharyngeal ganglia.

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\* A few days ago I saw a case of *Herpes Zoster Oticus and Pharyngis, with Facial Palsy, Hypoaesthesia, and Bradycardia* through the courtesy of Dr. Charles H. Peck. The eruption was distributed in the external auditory canal, the concha, antihelix, and the fossa of the antihelix of the right ear (Tympanum free). In addition there were herpetic vesicles and erosions limited to the right side of the soft palate. The posterior half of the dorsum of the tongue on the right side was also red and swollen, innervation of palate normal. Sensation was diminished on the entire right side of the face, head and neck. Right corneal reflex was absent. Herpetic pains were severe. Diagnosis Posterior poliomyelitis of the geniculate and glossopharyngeal ganglia.

17 Observation by Raynaud. Cited by Desnac, *Complications du Zona, Thèse de Bordeaux, 1903, p 20*

18 Chauveau, C. *Herpès du tympan avec un herpès guttural et labial, Ann d' mal de l'oreille, 1901, xxvii, 151*

CASE 18—Observation by Achard and Castaigne<sup>19</sup> A man, aged 51 Onset with pains followed by erythema of the left side of the face with an eruption of herpes zoster in all three branches of the left trigeminus, including its mucous membrane innervation In addition, herpetic vesicles were present on the left posterior pillar of the pharynx and left tonsil On depressing the tongue, vesicles were also evident on the left side of the pharyngeal vault There was no dysphagia and the eruption on the mucous membrane caused no pain, and was not perceived by the patient

*Comment*—This case is of interest because of the involvement of two ganglia, the Gasserian and the glossopharyngeal also as showing that true *intia aural* herpes zoster may cause no especial pain or discomfort to the patient and therefore may be readily overlooked

CASE 19—Observation by Haviland Hall<sup>20</sup> A man, aged 41 Onset Dec 27, 1906, with sore throat and dysphagia especially on the right side, the right tonsil and pillar of the fauces appeared red and swollen

December 29 Still pain in the throat, extending up into the right ear, the right side of the throat was red and swollen, and there were two or three yellow spots on the tonsil and posterior pillars of the fauces Temperature, 100 47

December 31 There was hoarseness and acute pain in the throat, shooting into the ear and entirely preventing sleep There was now a typical herpetic eruption on the right side of the soft and hard palate, extending to within an inch of the teeth, and sharply limited on the inner side, by the median raphe of the palate The larynx was normal

January 1 Euache worse and a group of vesicles appeared on the right edge of the tongue, extending from the pillar of the fauces to within one and a half inches of its tip

January 2 Patient still suffering much pain and three or four vesicles had made their appearance in the concha and below the helix of the right ear

January 3 The throat was easier and a few vesicles appeared on the right parietal and temporal region

January 6 There was general improvement, but the patient was still unable to take solid food

January 8 An attack of hiccough and vomiting The patient suffered from complete anorexia

January 9 Hiccough was very troublesome and there were only short intervals of relief

January 10 The hiccough was very severe and threatened to suffocate the patient, the paroxysms came on very rapidly with only about four or five seconds' interval One attack lasted three and a half hours

January 11 The hiccough ceased and frequent retching supervened

January 14 Retching and vomiting had gradually subsided and on January 15 solid food was taken

January 26 Patient was extremely prostrated and the throat was still painful with occasional stabs of pain through the right ear

*Comment*—This case is of unusual interest because of the combined auricular and *intia aural* herpes, corresponding to the zones of the geniculite and glossopharyngeal ganglia, but more especially because of the severe pneumogastric symptoms, anorexia, retching, vomiting and hiccough It will be observed that a period

19 Achard and Castaigne *Zona céphalique, Gaz hébd de méd et de clin*, 1897, new series, II, 1177

20 Hall, F de H *Herpes of Mucous Membrane and Skin*, Brit Med Jour, 1897, I, 848

of one week elapsed between the outbreak of the eruption and the appearance of the pneumogastric symptoms. This interval of quiescence separating the appearance of the eruption from the neural complications is of frequent occurrence in cases of geniculate inflammation with facial palsy.

### HERPES LARYNGIS AND ITS COMPLICATIONS

Posterior poliomyelitis of the root ganglia of the pneumogastric nerve is characterized by an eruption of herpes zoster in the auricular and intra-aural zones and in some cases by the occurrence of neural complications, such as bradycardia, nausea, vomiting and hiccup. These symptoms are due to involvement of the pneumogastric fibers passing through the inflamed ganglia.

**CASE 20—*Herpes Zoster Laryngis***—(Observation by Scheff<sup>21</sup>) A man aged 61. Onset July 28, with pain in the throat and hoarseness following exposure to cold, there was fever and difficulty in deglutition. Laryngological examination shows redness and swelling of the right arytenoid cartilage, right aryteno-epiglottidean fold and the right side of the epiglottis to the middle line with typical herpetic vesicles. The left side of the larynx was normal as were also the vocal cords, base of the tongue and fossa pyriformis. On July 30 and 31 pain and hoarseness continued with dyspnea and coughing. Examination showed the left side of the larynx still normal, the pharynx was normal but the uvula on its free end is somewhat edematous.

**CASE 21—*Herpes Laryngis***—(Observed by Stepanow<sup>22</sup>) A man aged 48, entered the hospital on April 7 for cough, difficulty and pain in swallowing. The onset had occurred on April 1 with stabbing pains in the neck.

April 8. Laryngoscopic examination. The left arytenoid cartilage was swollen and reddened on its inner surface as was also the left half of the epiglottis on its posterior aspect, on which were situated three small grayish white flecks, no other herpes visible.

April 14. Patient discharged cured.

**CASE 22—*Herpes Zoster Laryngis with Hiccup***—(Observation by Boulat<sup>23</sup>) A man, aged 50. Sudden onset February 29, with fever, headache, loss of appetite, general malaise and a sensation of discomfort in the throat. The general symptoms subsided but the discomfort, heat and irritation in the throat continued. It felt as if a foreign body were lodged behind the tongue, which the patient was unable to swallow, this was not a painful sensation but a perpetual discomfort and was accompanied by increased salivation and frequent movements of deglutition. This had made its appearance on the second day of the disease and was preceded twelve hours by a persistent and distressing hiccup, occurring every minute or half minute. This frequency was maintained until the fifth day of the disease. At no time was there difficulty with breathing or articulation, the voice was a little husky.

March 5. Laryngoscopic examination. The rhinopharynx was quite normal, the epiglottis is a uniform carmine red, but not edematous and was free from herpes on its anterior and superior surface. On its posterior aspect and solely on the left side there were six small grayish white spots which were isolated and regularly

21 Scheff, G. *Herpes Laryngis*, Wien med Ztschr., 1881, xxvi, 475.

22 Stepanow, E. M. *Herpes Laryngis*, Monatschr. f Ohrenh., 1885, xix, 237.

23 Boulat. *Herpes zosteriforme*, Arch. internat de laryngol., 1904, xviii, 149.

ound. The left arytenoid was slightly infiltrated, and presented four small grayish flecks, which were a little larger than those on the left posterior surface of the epiglottis. The vocal cords were slightly reddened.

March 9 The hiccup ceased and on March 10 the larynx had recovered its normal aspect. No vesicles were observed elsewhere.

#### *6 HERPES ZOSTER OF THE TONGUE WITH FACIAL PALSY*

Unilateral eruptions of herpetic vesicles on the tongue, in the distribution of the chorda tympani nerve, are occasionally observed in cases of peripheral facial palsy. In some of the observations the eruption preceded the paralysis, in others it appeared subsequently. In the latter group it is probable that the herpetic manifestations are secondary or neuritic in origin, in the former group, a primary lesion of the geniculate ganglion itself is not improbable. The question then naturally arises whether the geniculate has a splanchnic innervation within the buccal cavity in addition to its somatic representation on the external ear.

#### ANATOMIC CONSIDERATIONS

It is well known that the chorda tympani supplies the anterior two-thirds of the tongue with the sense of taste, its fibers springing from the cells of the geniculate ganglion. It has also been shown that, in some cases of facial palsy, the general sensibility of this region may also be obtunded, a fact long ago pointed out by Beinhardt. This would suggest that the chorda conveys some fibers of general sensation, as well as those subserving the special function of taste. Cushing's studies of the trigeminal field have shown that a crude sort of common sensation may persist on the anterior two-thirds of the tongue, after the Gasserian ganglion has been extirpated. This is further proof of the existence of such fibers. It is also worthy of mention in this connection, that the lingual branch of the seventh, which innervates the styloglossus and palatoglossus muscles at the base of the tongue, sends mucous filaments to the anterior pillars of the fauces and adjacent region. While it is true that this lingual branch has an anastomosis with the glossopharyngeal nerve, there is no proof that these mucous filaments are not part of the sensory facial system springing from the cells of the geniculate ganglion. The geniculate may therefore have a vestigial intra-oral sensory representation in addition to its taste function, as have the glossopharyngeal and vagus nerves, and that all three branchial nerves, the seventh, ninth and tenth are represented both in the mouth cavity and on the external ear.

In the lower vertebrate the intra-oral representations of these nerves are extensive and important, but in the course of phylogenetic development are being replaced by the overlap and growth of the trigeminus.

## CASES OF HERPES ZOSTER OF THE TONGUE WITH FACIAL PALSY

CASE 23—(Observation by Dr John J MacPhee of New York, unpublished) A man, aged 45. Exposure to cold followed by severe pain behind the left ear. This was accompanied by burning sensation on the left side of the throat and tongue. The pains were very severe and the patient was forced to remain indoors for several days, requiring liberal doses of codem. Later, there developed a left facial palsy, no disturbance of hearing. The sense of taste was lost on the anterior two thirds of the tongue on the affected side. Herpetic vesicles and erosions were present within this area, no vesicles were visible on the left side of the throat, although a distinct sensation of burning had been present in this region similar in character to that which was felt on the side of the tongue. No herpes in the ear or on the face. Later partial reactions of degeneration were present on the left side of the face. The ear pains were of unusual severity and persistence.

CASE 24—(Observation by Siegheim<sup>24</sup>) A man aged 72. Herpetic vesicles appeared on and behind the lobe of the right ear. A few days later a fresh crop of vesicles made their appearance on the right side of the tongue and hard palate. Eight days after the eruption the right side of the face became paralyzed.

CASE 25—(Observation by Bernack<sup>25</sup>) Pains in the right ear for eight days followed by a right facial paralysis with the palsy there appeared an eruption of herpes zoster on the anterior two thirds of the tongue. Sensations of tongue and taste were normal.

CASE 26—(Observation by Eichhorst<sup>26</sup>) Onset Dec 12 1906, after exposure to cold followed by pains in the right side of the face and neck. On the third day a right facial paralysis appeared and four days after the palsy, a herpetic eruption appeared on the lower half of the right auricle in the external auditory canal, and on the right side of the tongue the uvula and hard palate. Hearing normal, taste preserved, uvula not paretic.

CASE 27—(Observation by Remak<sup>27</sup>) A man aged 26. Onset Oct 22 1884, with pains in the right ear, followed on October 26 by a right facial paralysis. On October 29, an eruption of herpes appeared on the right border of the tongue in its anterior two thirds. Taste undisturbed, palate innervation normal. From November 10 to December 15, there was an excessive irritability of the auditory mechanism to sounds. Right face showed reactions of degeneration.

## 7 THE POSTERIOR POLYOMYELITIS OF THE AUDITORY GANGLIA

The peripheral ganglia of the auditory nerve are homologues of the posterior spinal ganglia. They take their origin from the neural ridge as the ganglion acusticum, and in common with other ganglia having this derivation, manifest a susceptibility to the specific inflammations of

<sup>24</sup> Siegheim Herpes zoster im Gebiete des Nervus facialis dexter, Monatsch f prakt Dermat., 1895, xx, 396

<sup>25</sup> Bernack Le paralysie faciale cité by Despaigne, Thèse de Paris, 1888

<sup>26</sup> Eichhorst, II Herpes zoster und Facialishämmung, Centralbl f inn Med., 1897, viii, 425

<sup>27</sup> Remak, E Zui Pathogenese des peripherischen Facialparalyse gelegentlich complic Herpes Zoster, Centralbl f Nervenheilk., 1885, viii, 145

herpes zoster (Fig 16) The cells composing the acoustic ganglia retain however, their primitive bipolar character, although recent investigations have shown that a few unipolar cells are demonstrable in man (Van Gehuchten<sup>28</sup>)

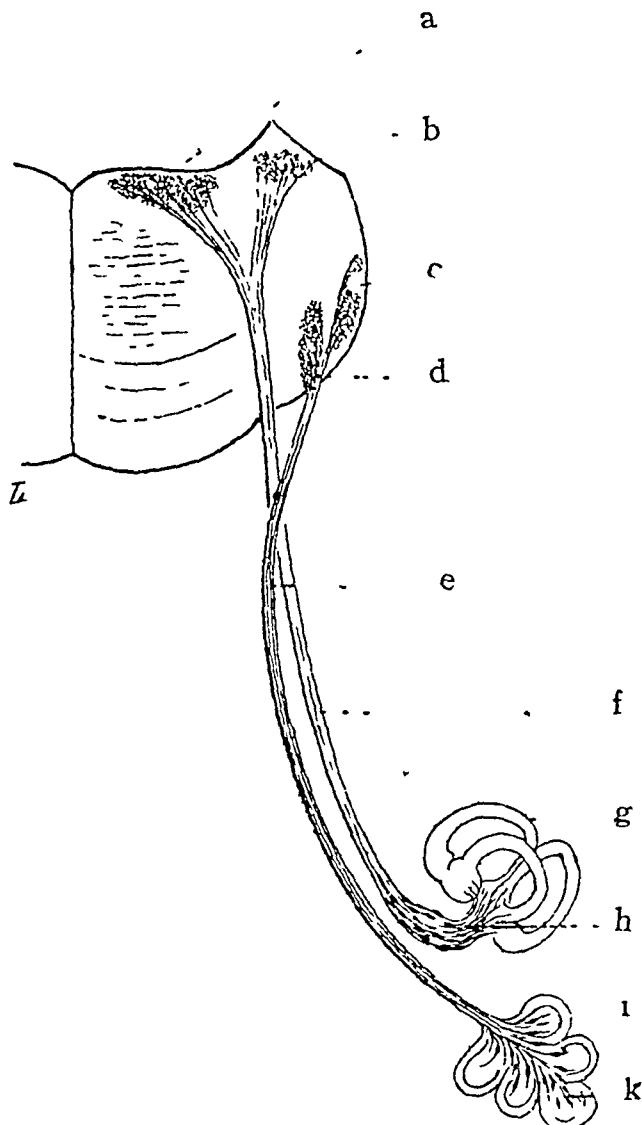


Fig 16.—The origin and termination of the acoustic nerve (a) nucleus posterior, (b) Deiters nucleus, (c) tuberculum acusticum laterale, (d) nucleus anterior, (e) nervus cochlearis, (f) nervus vestibularis, (g) semicircular canals, (h) ganglion of Scarpa, (i) cochlea, (k) ganglion spinale, or ganglion of Corti (Pommer and Charpy)

The ganglion acusticum at an early period separates into two ganglia the ganglion of Scarpa and the ganglion of Corti, or ganglion spinale,

<sup>28</sup> Van Gehuchten, A. Les cellules du ganglion de Scarpa chez l'homme adulte, La Névratre, 1907 8, 1x, 277

which are situated on the vestibular and cochlear divisions of the eighth nerve, respectively.

These ganglia are not infrequently involved in herpes zoster of the cephalic extremity, the symptoms of which vary according to the severity of the inflammatory reaction. In the milder form there are present only tinnitus aurium or a moderate degree of deafness (hypacusis). In the more severe forms, all the symptoms of Ménière's syndrome may occur i.e. labyrinthine deafness, disturbances of the equilibrium, nystagmus, nausea and vomiting.

It seems to me not improbable that some of these cases have been described as Ménière's disease also as toxic and "rheumatic" affections of the auditory nerve the few herpetic vesicles escaping notice or having disappeared before the patient came under observation.

In my series of eighty-seven cases of herpes zoster, with facial paralysis, auditory symptoms were present in twenty-six. The acoustic symptoms preceded the palsy in five cases in fourteen cases they appeared simultaneously. In the seven remaining cases the relationship is not mentioned, or was doubtful.

I would emphasize those cases in which the auditory symptoms appeared before the facial paralysis which show that the acoustic ganglia may be primarily involved, and are not secondarily affected by extension of the inflammatory process in the geniculate to the adjacent auditory nerve. It is, however, possible that such extension by contiguity may take place causing the auditory symptoms in some of these cases.

The distribution of the eruption and the nature of the acoustic disturbances in this group of cases were as shown in Table 1.

DISTRIBUTION OF ERUPTION AND NATURE OF ACOUSTIC DISTURBANCES IN POSTERIOR  
PORIONOMIMESIS OR THE AUDITORY GANGLIA

	Tinnitus Aurium	Hyper- acusis	Hyp- acusis	Ménière's Syndrome
Herpes facialis			3	2
Herpes facialis and oticus com- bined			1	
Herpes oticus		1	2	2
Herpes occipito collaris	2		9	1
Herpes occipito collaris and oticus combined			2	1

Auditory symptoms may also accompany zona of the cephalic extremity without facial paralysis. This group of cases is additional proof of primary involvement of the acoustic ganglia, as it would be difficult to conceive of an inflammatory process in the geniculate ganglion passing over to the eighth nerve without involving the motor fibers of the seventh

TABLE 2—DISTRIBUTION OF THE ERUPTION AND NATURE OF THE ACOUSTIC DISTURBANCES IN CEPHALIC ZONA WITHOUT FACIAL PALSY

Herpes facialis with tinnitus and hypoacusis	2 cases
Herpes oticus with tinnitus and hypoacusis	4 cases
Herpes occipito collaris with Ménière's syndrome	1 case

Escarat,<sup>29</sup> in a recent communication, records 3 cases of auditory disturbances in herpes zoster of the face, in one of which facial palsy was also present. These auditory symptoms, he believes, are produced either by a tryponeurosis of the tubo-tympanic membrane or by a paralysis of accommodation, due to involvement of the tensor tympani. This explanation, however, is applicable only to a limited group of cases, in which the fifth nerve is the seat of the eruption, and the symptoms indicate an involvement of the conduction mechanism of the ear.

#### POSTERIOR POLIOMYELITIS OF THE AUDITORY GANGLIA WITHOUT HERPES ZOSTER

If the auditory ganglia may be primarily involved in zona, in conjunction with an eruption in one or more of the zones of the cephalic extremity, may there not exist a group of cases in which these ganglia are alone affected, without eruptive manifestations?

The pathological studies of Head and Campbell have shown that the inflammatory process underlying herpes zoster is commonly localized in a single ganglion, and as the acoustic ganglia belong genetically to the spinal chain, and clinically are frequently involved in zona, it would seem reasonable to assume that the local inflammatory reactions may be confined to these ganglia in certain cases. The clinical picture would then be characterized by the general symptoms and mode of onset of zona, but the eruptive manifestations would be replaced by symptoms indicating a more or less severe involvement of the cochlear and vestibular divisions of the auditory nerve. It is not improbable that cases answering this description have been considered under the heading of primary "rheumatic" affections of the eighth nerve. In the absence of definite pathological evidence, absolute proof of the existence of such a group is impossible. The demonstration of a lymphocytosis in the cerebrospinal fluid would, however, be of great diagnostic value in doubtful cases, because of its frequent occurrence in herpes zoster.

29 Escarat Troubles otiques fonctionnelles et trypotiques dans le zona total ou partiel du tempémore, Bull de Laryngol, Otol et Rhinol, 1908, vi, 173.

### 8 THE PARALYTIC COMPLICATIONS OF HERPES ZOSTER FACIALIS AND OCCIPITOCOLLARIS

Facial palsy and auditory symptoms are also frequent complications of herpes facialis and herpes occipitocollaris. Such neural complications occurring when the eruption is situated in the trigeminal or upper cervical zones, are, I believe, produced by inflammatory reactions in the geniculate and auditory ganglia (multiple involvement of ganglia in zona). In my series of cases the eruption was distributed in the zones of the trigeminal or upper cervical ganglia, in by far the larger proportion of cases.

Herpes occipitocollaris with facial palsy was noted in forty-eight cases. There was an associated hypacusis in nine, tinnitus aurium in two, and Ménière's syndrome in one case of this group.

Herpes facialis with facial palsy was observed in fifteen cases, of which three had an associated hypacusis and two presented the symptoms of Ménière's disease.

#### REPORT OF PERSONAL CASES

**CASE 28—*Herpes Occipitocollaris with Facial Palsy***—(Referred by Dr Theodore Janeway, St. Luke's Hospital.) A woman, aged 45. Onset June 9, 1909, with pains in the neck. On June 10 there appeared a widespread herpetic eruption in the right occipitocephalic distribution (second, third and fourth cervical) with great swelling and redness of the integument. During the first few days of the disease there was tinnitus aurium. On June 17 the right side of the face was paretic, palate innervation, taste and hearing were normal. On June 18, the facial palsy was complete, severe pain and burning in the eruptive area.

July 7, the eruption had disappeared, but the facial palsy still persisted, no auditory symptoms (Fig. 17).

**CASE 29—*Herpes Zoster Occipitocollaris with Facial Palsy***—(Referred by Dr C. A. MacWilliams.) A man, aged 71, in good health. Onset Oct. 26, 1907, with an eruption of herpes zoster on the left side of the head and neck. The eruption was accompanied by smarting pain. On November 4, the patient first noted a buzzing sensation in the left ear. This was not severe and did not last very long, and was followed by a left facial palsy. Examination showed typical peripheral facial palsy on the left side, complete in the lower and middle branches, partial in the upper branch, increased lacrimation of the left eye. Palate innervation, normal. The herpetic eruption was distributed over the occiput and neck on the left side. There were no sensory disturbances of the face or neck, with the exception of slight hypalgesia in the eruptive area. The corneal reflex was present on both sides. Hearing was good in both ears, but was not so distinct in the left as in the right. This was true of both the watch and tuning fork. The patient recognized salt, sweet and sour on the left side of the tongue in the chorda area, but these sensations were not so prompt or so distinct as on the right side. Faradization of the left facial nerve produced a slight contraction in the orbicularis palpebrae and frontalis on the left side, but practically no response in the lower branches. Direct faradization of the muscles of the left face produced a slight response in the muscles of the upper but none in those of the lower face. Post herpetic pains were very mild and all trace of the palsy disappeared within a month.

CASE 30.—*Herpes Zoster Occipitocollaris with Facial Palsy*—(Referred from the Hudson Street Hospital service of Dr Conner.) A man, aged 60, with spastic paraplegia of many years' duration of syphilitic origin. Onset of present illness, Feb 19, 1906, with sharp shooting pains in the right side of the neck, occiput and mastoid region. A few days later an herpetic eruption appeared in the right occipitocephalic distribution. A right facial palsy developed within a week after the appearance of the eruption. There were no subjective disturbances of taste or hearing at the time of onset. The eruption cleared up in a few days, leaving numerous pigmented scars. Severe shooting pains with burning and itching still persisted.

On examination, May 16, 1906, there was still evident a right facial palsy but with slight power of voluntary movements in all of the branches. Innervation



Fig 17 (Case 30).—*Herpes occipitocollaris with facial palsy on the affected side*

of the palate was equal on the two sides, hearing was normal. Sensation of taste, while subjectively unimpaired, showed a distinct diminution when tested with solutions of salt, sugar and quinin. There were numerous areas of diminished sensation scattered over the right side of the neck and angle of the jaw, which correspond to the pigmented areas. Electrical examinations showed partial reactions of degeneration of the muscles of the right face.

June 20, 1906, there were still numbness and itching sensations in the right occipitocephalic region with diminished sensibility. Lancinating pains were still present, but less severe and frequent. Taste was still obtunded on the right side.

Voluntary innervation of the face had improved, especially in the upper branches, in the lower branches beginning contracture was apparent. Partial reaction of degeneration still present.

**CASE 31—*Herpes Zoster Facialis with Facial Palsy and Deafness***—(Observation by Kaufmann<sup>30</sup>) A man aged 34. Mild prodromal symptoms with fever and headache. On July 25, redness of the left cheek and an eruption of herpes zoster, accompanied by headache, vertigo and repeated vomiting. July 26, still headache and repeated vomiting. July 29, sudden development of a left facial palsy with tinnitus and total deafness of the left ear. Palate normal, taste lost. August 24, patient had no vertigo but constant tinnitus in the left ear. August 27, the facial palsy had cleared up but vertigo and disturbances of the equilibrium were still present. November 5, patient had recovered but with tinnitus and some diminution of hearing on the affected side.

**Comment**—The occurrence of repeated vomiting before the onset of the auditory disturbances in this case suggests a probable involvement of the fibers of the vagus.

#### CONCLUDING REMARKS

From the evidence which has been presented, I believe that we are justified in isolating a large and varied group of cases, characterized by herpes zoster of the cephalic extremity associated with facial palsy, auditory, glossopharyngeal, and pneumogastric symptoms, and in regarding them as constituting a well-defined clinical picture. A number of syndromes are thus united in a symptom-complex, having a common etiology and pathology.

The neural complications may occur singly, or in various combinations, depending on the degree of the infection and the localization of the inflammatory process. Because of the tendency to invasion of more than one ganglion in cephalic zona, neural complications may occur even when the eruption is situated in the distribution of a ganglion situated above or below that causing the paralysis. In this event the nerve complication is caused by an inflammatory reaction in the ganglion of the affected nerve sufficient to cause a transient palsy, but not to produce an eruption.

The general symptoms may be very mild, or they may reach a high degree of severity, in consequence of which a considerable variation in the clinical picture results.

The neural symptoms are often singularly transient in their duration, all trace disappearing within a few days or a fortnight. Not infrequently permanent structural changes take place with persistent disturbance of function.

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<sup>30</sup> Kaufmann, D. Ueber ein Fall von gleichseitiger, acut aufgetretenen Erkrankungen des Acusticus, Facialis und Trigeminus, *Ztschr f Ohrenh*, 1896-7, xxx, 125.

As is well known, patalectic complications may occur in other parts of the body in zona, notably of the oculai nerves, but also in the distribution of the spinal nerves. These are, comparatively speaking, rare, probably because the inflammatory lesions are limited by the capsule of the ganglion, and in order to reach the motor nerves of the eye in Gasserian involvement, or the anterior root in that of the spinal ganglia, the inflammation must first break through this fibrous wall, or travel for some distance along the course of the sensory nerve. The capsule of the ganglion, therefore, forms a natural barrier and protection against the extension of the inflammatory process.

Anatomical conditions are different, however, in the ganglia under consideration. Here the fibers of the seventh, eighth, ninth and tenth nerves are in more immediate relation to the cell structures of their respective ganglia, and are not separated by an intervening fibrous wall.

For this reason very slight inflammatory reactions within these ganglia jeopardize their respective nerve fibers. This intimate association of ganglionic structure and nerve fibers would account, not only for those cases with light and transient symptoms, but also for those of a more severe grade, with lasting impairment of function.

In my study of this group of cases, I have encountered none in which a fatal issue could be attributed directly to the disease itself. It is well known that a unilateral lesion or section of the vagus is not necessarily dangerous to life, and as herpes zoster is usually unilateral pneumogastric involvement on one side would not be fatal. If, however, bilateral zona of the cephalic extremity should occur, involving the ganglia of the pneumogastric nerves on both sides dangerous symptoms, or even a fatal termination might result. It is perhaps significant in this connection to recall the wide-spread belief among the laity of the fatal tendency of bilateral shingles. Possibly we have here an explanation for a tradition which is common to all nations.

I would also emphasize the fact that in my study of this subject, I have found no cases with facial, auditory, glossopharyngeal or pneumogastric nerve complications, accompanying an eruption of herpes zoster, except when situated on the cephalic extremity of the body, i.e., herpes facialis, oticus, pharyngis, laryngis, lingualis, and occipitocollaris. That such neural complications do not accompany an eruption in the lower segments of the body is readily understood from the tendency of the posterior poliomyelitis to limit itself to a small series of ganglia usually only one or two. In severe forms of infection, however, with extensive involvement of the cerebrospinal chain of ganglia there is no reason, theoretically, why cranial nerve palsies may not occur.

I have attempted to differentiate the somatic zones of the geniculate, glossopharyngeal, and vagal ganglia on the external ear, as well as their intraoral, splanchnic zones within the buccal cavity. The demarcation of these zones is, however, only a preliminary one. It will, I hope direct attention to the subject and may prove of value as a guide in future investigations. I believe that we have in the "herpes zoster method" an important key to the solution of this intricate problem.

It is my firm conviction that cases belonging to the group which I have just described are of much more frequent occurrence than might be inferred from the study of our literature. The reasons for which are to be found in the smallness and inaccessibility of the eruptive areas, making their detection difficult, or all traces of the eruption may have disappeared before the case comes under observation, when a retrospective diagnosis might be difficult or impossible.

It also seems probable, that some cases which are interpreted as rheumatic palsies of the face, palate and even the larynx, may belong to this group, as well as toxic unilateral palsies of obscure origin. This, I believe is also true of unilateral affections of the auditory nerve.

It is interesting to note, in this connection, that herpes zoster may apparently occur in an abortive form (Widal<sup>31</sup>), running its course with mild general symptoms and a few neuralgic pains, but without the characteristic eruption. In cases of this doubtful nature, as well as in those rheumatic affections of the facial and auditory nerves accompanied by neuralgic symptoms and localized neuralgic pains the demonstration of a lymphocytosis of the cerebrospinal fluid would have a considerable diagnostic value, as recent investigations have shown that these are frequently increased in herpes zoster.<sup>32</sup>

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